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(54) Title: NOVEL COMPOUNDS

(57) Abstract

This invention pertains to novel compounds which are derivatives of phosphonoformic acid, processes for their synthesis and their use as antiviral agents.

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NOVEL COMPOUNDS

Field of the invention

The present invention relates to novel compounds, novel methods for their preparation, novel intermediates, pharmaceutical compositions and to methods for combatting viral diseases caused by, for example, herpesviruses or retroviruses, which can occur in animals including man. Such diseases include both common viral infections and virus-related neoplastic diseases.

Background of the invention

Phosphonoformic acid (PFA) is a well known compound having antiviral activity. Pharmaceutical formulations of PFA for the treatment of viral diseases have been described in U.S. Patent Nos. 4,215,113; 4,339,445; 4,665,062 and 4,771,041. PFA inhibits replication of all known herpesviruses in vitro including cytomegalovirus (CMV), herpes simplex virus types 1 and 2 (HSV-1, HSV-2), human herpesvirus 6 (HHV-6), Epstein-Barr virus (EBV) and varicella-zoster virus (VZV) as well as certain retroviruses including the human immunodeficiency virus (HIV) types 1 and 2 (HIV-1 and HIV-2).

Alkyl derivatives of PFA are known from EP 0 003 007 and from Norén, J.-O. et al. (J. Med. Chem. 26 (1983) 264-270) and amide derivatives of PFA are known from EP 0 003 008, as are the antiviral effects in vitro and in vivo in animals of such compounds and of pharmaceutical compositions thereof. So far, however, no drug based on any of these alkyl or amide derivatives has become availiable.

Phosphonoformic acid hydrazides are known from US 4,308,263 as are the antiviral effects against herpesviruses in vitro of such compounds. So far, however, no drug based on any of these hydrazides has become available.

Lipid derivatives of phosphonoacids for liposomal incorporation are known from WO 95/13682 and from Hostetler, K. Y. et al., Antiviral Research 31 (1996), 59-67, as are the antiviral effects in vitro of such compounds on viruses such as HIV, hepatitis B virus, EBV, and VZV.

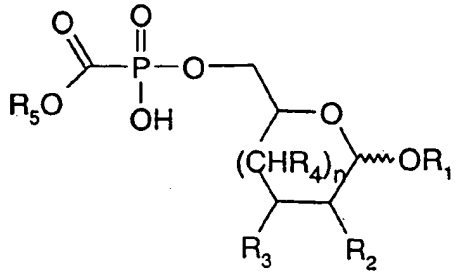
P-monoesters of foscarnet with octadecyl substituted alditol moieties as well as with substituted derivatives of glycerol have been disclosed in WO 96/15132.

Treatment of CMV infections in AIDS patients infected with herpesvirus with foscarnet, i.e. trisodium phosphonoformate hexahydrate, is at present by intravenous injections. This mode of treatment is burdensome where foscarnet must be administered daily. Doses in the range of grams per day need to be administered. The development of a more effective drug is therefore very desirable since it would offer a more convenient method of treatment and result in improved quality of life for the patient.

Description of the invention

The compounds

According to the present invention we provide compounds of formula I



I

wherein the wavy line signifies a bond which is either in the α- or in the β-configuration;

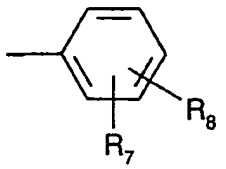
n is 0 or 1;

R_1 is C_{1-24}-alkyl, C_{2-24}-alkenyl, C_{2-24}-alkapolyenyl containing 2 to 6 double bonds, C_{2-24}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-24}-alkyl, or C_{1-12}-alkoxy-C_{1-12}-alkyl group, all of which may be branched or unbranched and all of which may be optionally substituted with hydroxy, amino, halogen, or oxo;

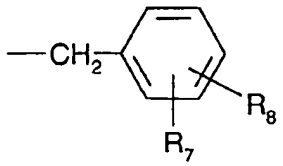
R_2, R_3 and R_4 are each independently hydrogen, halogen, amino, acetylamino, azido, or a group XR_6 wherein X is O or S and R_6 is hydrogen, or a branched or unbranched C_{1-4}-alkyl or C_{2-4}-alkenyl group both of which may be optionally substituted with hydroxy, amino, halogen, or oxo, or

R_2, R_3, and R_4 together with the respective geminal hydrogen represent an oxo group;

R_5 is hydrogen, or a group of the formula II or III,



II



III

wherein R_7 and R_8 are the same or different and are bound to any two positions of the phenyl ring and each is selected from the group consisting of hydrogen, halogen, or C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-acyl, C_{1-4}-acyloxy, C_{2-5}-alkoxycarbonyl all of which may be branched or unbranched; or R_7 and R_8 together form an unbranched saturated alkylene chain having 3 or 4 carbon atoms bound to adjacent positions in the phenyl ring; or R_7 and R_8 together form a methylenedioxy group, a 1,1-ethylidenedioxy group, or a 1,2-ethylenedioxy group bound to adjacent positions in the phenyl ring,

or R_5 is a group $R_9COOCHR_{10}-$ or a group $R_9OCOOCHR_{10}-$

wherein R_9 is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, or C_{1-6}-alkoxy-C_{1-6}-alkyl group all of which may be branched or unbranched, and all of which may be optionally substituted with hydroxy, amino, halogen, or oxo; and R_{10} is hydrogen or a branched or unbranched C_{1-4}-alkyl group;

and wherein the configurations of the substituents R_2, R_3, R_4 and $R_5OOCPO(OH)OCH_2$- in I independently are D-gluco, L-gluco, D-galacto, L-galacto, D-manno, L-manno, D-talo, L-talo, D-allo, L-allo, D-altro, L-altro, D-gulo, L-gulo, D-ido, or L-ido when n is 1, or that the configurations of the substituents R_2, R_3 and $R_5OOCPO(OH)OCH_2$- in I independently are D-ribo, L-ribo, D-arabino, L-arabino, D-xylo, L-xylo, D-lyxo, or L-lyxo when n is 0;

and physiologically acceptable salts and optical isomers thereof.

The configuration of the glycosidic bond of the compounds of the present invention is preferably α.

Preferred compounds of formula I are those wherein R_1 is a C_{9-24}-alkyl, C_{9-24}-alkenyl, C_{9-24}-alkapolyenyl containing 2 to 6 double bonds, C_{9-24}-alkynyl, C_{3-8}-cycloalkyl-C_{6-24}-alkyl, or C_{1-12}-alkoxy-C_{8-12}-alkyl group all of which may be branched or unbranched and all of which may be optionally substituted with hydroxy, amino, halogen, or oxo.

Especially preferred compounds of formula I are those wherein R_1 is *n*-tetradecyl, *n*-octadecyl, *trans*-9-octadecen-1-yl, or *cis*-9-octadecen-1-yl. Preferably also R_2, R_3, and R_4 are each a hydroxyl group. It is also preferred for R_5 to be H. Additionally, it is preferred for n to be 1. Even more preferred are compounds of formula I wherein the configuration of R_2, R_3, R_4, and $R_5OOCPO(OH)OCH_2$- is D-gluco.

The compounds of the invention are useful in therapeutic and /or prophylactic treatment of viral infections and may be useful in therapeutic and/or prophylactic treatment of virus-related neoplastic diseases in mammals.

The compounds of the present invention are particularly useful for the treatment of human herpesvirus infections and human retrovirus infections. They are also useful for the treatment of viral infections associated with acquired immunodeficiency syndrome (AIDS). The human herpesviruses include HSV-1 and HSV-2, VZV, CMV, EBV, human

herpesvirus 6 and 7(HHV-6 and HHV-7), and human herpesvirus 8 (HHV-8) also known as Kaposi's sarcoma associated herpesvirus (KSHV). Human retroviruses include human immunodeficiency virus type 1 and 2 (HIV-1 and HIV-2) and human T-cell leukaemia virus type 1 and type 2 (HTLV-1 and HTLV-2). Another important area of use of the compounds of the present invention is in the treatment of infections caused by orthomyxoviruses, e.g. influenza viruses of type A and type B. A further area of use is in the treatment of infections caused by viruses such as hepatitis B virus and hepatitis C virus, papillomaviruses, adenoviruses and poxviruses.

Other possible areas of use of the compounds of the present invention are in the treatment of infections caused by picornaviruses, arboviruses, arenaviruses, coronaviruses, rhabdoviruses, paramyxoviruses and bunyaviruses.

Pharmaceutical formulations

The compounds according to the invention may be used for the therapeutic and prophylactic control and treatment of diseases caused by virus infections. The compounds of the invention can be used alone or with other antiviral agents, e.g. acyclovir, valacyclovir, famciclovir, penciclovir, desciclovir, brivudine, carbovir, fiacitibine, ibacitabine, ganciclovir, idoxuridine, sorivudine, trifluridine, vidarabine, cidofovir, lobucavir, afovirsen, zidovudine, didanosine, stavudine, zalcitabine, dideoxyadenosine, lamivudine, FTC, fialuridine, adefovir, adefovir dipivoxil, nevirapine, delaviridine, loviride, saquinavir, indinavir, ritanovir, nelfinavir, 141W94, ribavirin, amantidine, rimantidine, sICAM-1, pirodavir, GG167, 1263W94, fomivirsen, GEM-132, RS-79070, SR-3775, or with immunological agents e.g. antiinflammatory agents including steroids, in particular glucocorticoids, and non-steroid antiinflammatory drugs (NSAID's), CMV neutraGAM, regavirumab, sevirumab, interferon, and growth factors e.g. granulocyte-macrophage (GM-CSF) and granulocyte-colony stimulating factors (G-CSF).

The compounds of the present invention are suitably admixed with excipients to be formulated into capsules, tablets, suppositories and other formulations, e.g. ointments, suspensions, gels and solutions.

For clinical use the compounds of the invention may be formulated into pharmaceutical formulations for oral, parenteral, rectal and topical administration. The pharmaceutical formulation contains the compound of the invention normally in combination with a pharmaceutically acceptable excipient. The excipient may be in the form of a solid, semi-solid or liquid diluent. Usually the amount of active compound is between 0.1-99% by weight of the preparation.

In the preparation of pharmaceutical formulations containing the compounds of the present invention in the form of dosage units for oral administration the compound may be mixed with a solid, powdered carrier, e.g. lactose, sucrose, sorbitol, mannitol, starch, amylopectin, cellulose derivatives, gelatin, or another suitable carrier; stabilizing substances, e.g. alkaline compounds, e.g. bicarbonates, carbonates, and hydroxides of sodium, potassium, calcium, magnesium, as well as magnesium oxide and the like as well as with lubricating agents e.g. magnesium stearate, calcium stearate, sodium stearyl fumarate and polyethyleneglycol waxes. The mixture may then be processed into granules or pressed into tablets. Granules and tablets may be coated with an enteric coating which protects the active compound from acid catalyzed degradation as long as the dosage form remains in the stomach. The enteric coating is chosen among pharmaceutically acceptable enteric-coating materials e.g. beeswax, shellac or anionic film-coating polymers and the like, if preferred in combination with a suitable plasticizer. To the coating various dyes may be added in order to distinguish among tablets or granules with different active compounds or with different amounts of the active compound present.

Soft gelatin capsules may be prepared with capsules containing a mixture of the active compound of the invention, vegetable oil, fat, or other suitable vehicle for soft gelatin capsules. Soft gelatin capsules may also be enteric-coated as described above.

Hard gelatin capsules may also contain the active compound in combination with a powdered carrier as described above. The hard gelatin capsules may be enteric-coated as described above. Hard gelatin capsules may contain granules or enteric-coated granules of the active compound.

Dosage units for rectal administration may be prepared in the form of suppositories with the active substance mixed with a neutral fat base, or they may be prepared in the form of a gelatin capsule which contains the active substance in a mixture with a vegetable oil, paraffin oil or other suitable vehicle for gelatin rectal capsules, or they may be prepared in the form of enemas, e.g. dry micro enemas, or they may be reconstituted in a suitable solvent just prior to administration.

Liquid preparations for oral administration may be prepared in the form of solutions, syrups, emulsions or suspensions, e.g. containing from 0.1% to 50% by weight of the active ingredient and the remainder consisting of for example sugar or an alditol and/or a mixture of ethanol, water, glycerol, propylene glycol and/or polyethylene glycol. If desired, such liquid preparations may contain colouring agents, flavouring agents, saccharin or carboxymethyl cellulose or other thickening agents. Liquid preparations for oral administration may also be prepared in the form of a dry powder to be reconstituted with a suitable solvent prior to use.

In addition, using known pharmaceutical procedures, sustained release preparations at doses of 1 mg to 2000 mg may be formulated.

For topical application, especially for the treatment of herpes virus infections on skin, genitals and in mouth and eyes the preparations are suitably in the form of a solution, ointment, gel, suspension cream or the like. The amount of active substance may vary, for example between 0.05% to 20% by weight of the preparation . Such preparations for topical application may be prepared in known manner by mixing the active substance with

known carrier materials e.g. isopropanol, glycerol, paraffin, stearyl alcohol, polyethylene glycol, etc. The pharmaceutically acceptable carrier may also include a known chemical absorption promotor. Examples of absorption promotors are e.g. dimethylacetamide, trichloroethanol or trifluoroethanol, certain alcohols and mixtures thereof.

Liposomal formulations based on lipid substances, e.g. phospholipids, sphingolipids, glycolipids, and galactolipids can be used for formulations for oral, topical or parenteral administration.

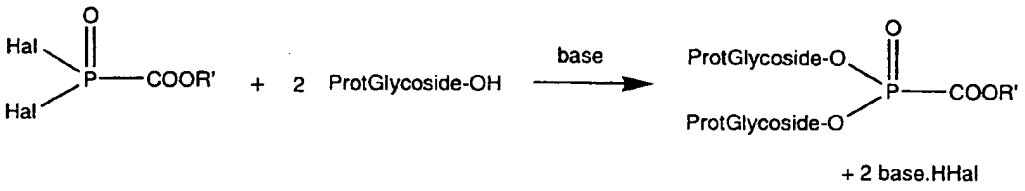
The typical daily dose of the active substance will depend on various factors such as for example the individual requirement of each patient, the route of administration and the disease. In general, doses will be in the range of 1 mg to 2000 mg per day, preferably 5 mg to 1000 mg of active substance per day. Unit doses of 0.25 mg to 2000 mg can be given e.g. 1 to 4 times a day.

Methods of preparation of the compounds of the invention, starting materials and intermediates.

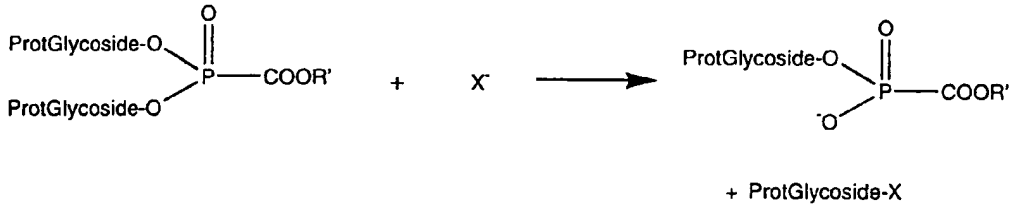
Some of the compounds of the formula I may be prepared from triesters or P,C-diesters of phosphonoformic acid in which suitably protected glycoside moieties are present as P,P-diesters or P-monoesters, respectively, which are deprotected in a final step to give the compounds of formula I. The compounds of the formula I may be prepared by methods analogous to known methods for the synthesis of either diesters or monoesters of phosphonic acids, for example as described in Houben-Weyl, Methoden der Organischen Chemie, Auflage 4, Band XII, Teil 1, Organischen Phosphorverbindungen, p. 408-414 and 423-463. Examples of such methods are the following.

A. Reacting an alkoxycarbonylphosphonic dihalide or an aryloxycarbonylphosphonic dihalide with at least two equivalents of a glycoside ProtGlycoside-OH, which may if

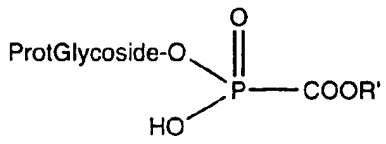
necessary be suitably protected, with a free hydroxyl group at the 6-position if a hexose or at the 5-position if a pentose in the presence of a base such as, for example, pyridine or triethylamine, according to the formula:



followed by selective removal of one of the glycoside groups, e.g. by reaction with iodide or bromide anion according to the formula:

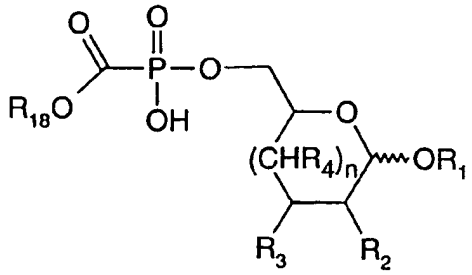


The resulting intermediate compound of the formula



IVa

is then, where necessary, subjected to deprotection of the glycoside moiety, if desired with concomitant or subsequent removal of R', to give a compound of the formula IVb, e.g. in the form of a salt thereof



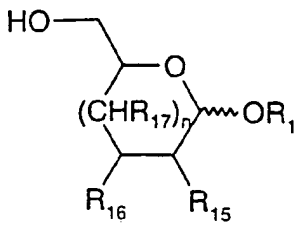
IVb

wherein n, R_1, R_2, R_3, and R_4 have the meaning given above, R' has the meaning given above for R_5 with the exception of hydrogen, or R' is branched or unbranched C_{1-6} alkyl, R_{18} is R' or hydrogen,

X is Br or I and Hal is Cl, Br or I

In the case where R_{18} is R_5, the compounds of the formula IVb correspond to compounds of the formula I.

ProtGlycoside-OH corresponds to a compound of the formula V



V

wherein n and R_1 are as defined above, and R_{15}, R_{16} and R_{17} each correspond to the groups R_2, R_3 and R_4, respectively, which have, when necessary or desired, been derivatized by suitable protective groups. Preferred protective groups are methoxymethyl, methylthiomethyl, benzyloxymethyl, *p*-methoxybenzyloxymethyl, tetrahydropyranyl, 1-ethoxyethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl, *t*-butyl, allyl, but-2-enyl, 3-methylbut-2-enyl, *p*-methoxyphenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *p*-nitrobenzyl, diphenylmethyl, trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, acetyl, chloroacetyl, trifluoroacetyl, propionyl, isobutyryl, pivaloyl, benzoyl, *p*-methoxybenzoyl, *p*-chlorobenzoyl, *p*-bromobenzoyl, 2,2,2-trichloroethoxycarbonyl, methanesulfonyl or *p*-toluenesulfonyl in the case where at least one of the groups R_2, R_3 and R_4 is a hydroxyl group or R_6 is substituted by a hydroxyl group, or ethylidene, isopropylidene, cyclohexylidene, benzylidene, *p*-methoxybenzylidene, methoxymethylene, ethoxymethylene, di-*t*-butylsilylene, or tetraisopropyldisiloxane-1,3-diylidene in the case where at least two of groups R_2, R_3 and R_4 are hydroxyl groups, or methoxymethyl, benzylthiomethyl, phenylthiomethyl, tetrahydropyranyl, 2-cyanoethyl, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, diphenylmethyl, *t*-butyl, acetyl, benzoyl, 2,2,2-trichloroethoxycarbonyl, *t*-butoxycarbonyl or benzyloxycarbonyl in the case where at least one of the groups R_2, R_3 and R_4 is a thiol group, or ethoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, *t*-butoxycarbonyl, allyloxycarbonyl, benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, formyl, chloroacetyl, trichloroacetyl, trifluoroacetyl, phthaloyl, allyl, 2-trimethylsilylethoxymethyl, benzyl, benzylidene or *p*-methoxybenzylidene in the case where at least one of the groups of the groups R_2, R_3 and R_4 is an amino group or R_6 is substituted by an amino group, or finally, in the case where one of the groups R_2, R_3 and R_4 together with the respective geminal hydrogen represent oxo, or R_6 is substituted by an oxo group, then the group is derivatized as e.g. a dimethyl ketal, a bis(2,2,2-trichloroethyl) ketal, a dibenzyl ketal, a diacetyl ketal, a 1,3-dioxane, a 5-methylene-1,3-dioxane, a 1,3-dioxolane, a S,S'-dimethyl dithioketal, a S,S'-dibenzyl dithioketal, a S,S'-diacetyl dithioketal, a 1,3-dithiane, a 1,3-dithiolane, a 1,3-oxathiolane, an O-acetyl cyanohydrin, an O-trimethylsilyl cyanohydrin, an N,N-dimethylhydrazone, a 2,4-dinitrophenylhydrazone,

an oxime, or an O-methyloxime and salts and optical isomers thereof. Further examples of suitable protective groups for the functional groups of the glycoside moiety are given in Protective Groups in Organic Synthesis, Ed. T. W. Greene and P.G. M Wuts, John Wiley & Sons, Inc., New York, 1991 (Ref. 1).

Novel starting materials are compounds of the formula ProtGlycoside-OH corresponding to formula V, wherein R_1 is a C_{9-24}-alkyl, C_{9-24}-alkenyl, C_{9-24}-alkapolyenyl containing 2 to 6 double bonds, C_{9-24}-alkynyl, C_{3-8}-cycloalkyl-C_{6-24}-alkyl, or C_{1-12}-alkoxy-C_{8-12}-alkyl group, all of which may be branched or unbranched and all of which may be optionally substituted with hydroxy, amino, halogen, or oxo;

provided that in the case where the configuration of the substituents R_{15}, R_{16} , R_{17} and $HOCH_2$- is D-gluco,

i) R_1 is not *n*-decyl, *n*-dodecyl, or *n*-octadecyl at the same time as each of R_{15}, R_{16} and R_{17} is benzyloxy, and

ii) R_1 is not 1-ethenyl-1,5-dimethyl-4-hexen-1-yl at the same time as each of R_{15}, R_{16} and R_{17} is benzoyloxy, and

iii) R_1 is not 8-hydroxy-1-(4-hydroxy-2-methyl-2-butenyl)-3,7-dimethyl-2,6-octadienyl at the same time as R_{15} is 2-methyl-2-butenoate and each of R_{16} and R_{17} is acetoxy, and

provided that, in the case where the configuration of the substituents R_{15}, R_{16} , R_{17} and $HOCH_2$- is D-galacto,

iv) R_1 is not *n*-octadecyl at the same time as each of R_{15} , R_{16} and R_{17} is acetoxy, and

provided that, in the case where the configuration of the substituents R_{15}, R_{16} , R_{17} and $HOCH_2$- is D-manno,

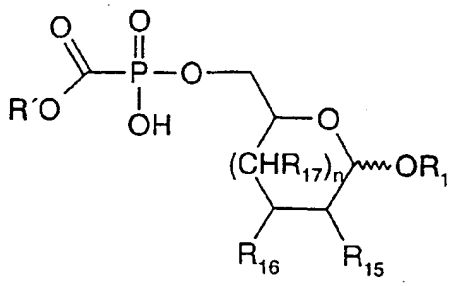
v) R_1 is not *n*-hexadecyl at the same time as each of R_{15} , R_{16} and R_{17} is trimethylsilyloxy, and

vi) R_1 is not 3,7,11-trimethyl-2,6,10-dodecatrienyl at the same time as each of R_{15} , R_{16} and R_{17} is acetoxy,

and salts and optically active isomers thereof.

Said preferred starting materials for the first step of the synthesis are novel and comprise part of the present invention.

The compounds of the formula IVa which correspond to compounds of the formula VI, wherein n, R_1, R_{15}, R_{16}, R_{17} and R'are as above, and physiologically acceptable salts and optical isomers thereof are novel and comprise part of the present invention.



VI

The first step of the synthesis is performed by methods known *per se* for the phosphorylation of alcohols by phosphoric and phosphonic dihalides. Examples of such methods are described for example in Slotin, L.A. in Synthesis 1977, 737 (Ref. 2) and Seliger, H. and Kössel, H., Progress in the Chemistry of Organic Natural Products 32 (1975) 297 (Ref. 3). The alkoxycarbonyl- and aryloxycarbonylphosphonic dihalides are

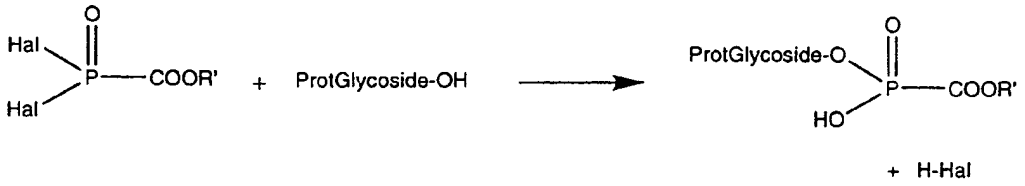
prepared by methods known *per se* for the synthesis of dihalides of phosphoric acids and phosphonic acids. References for these methods are found, for example, in the two publications above and in Houben-Weyl, Methoden der Organischen Chemie, Auflage 4, Band XII/1, p. 387-406 and Band XII/2, p. 212-225.

The second step of the synthesis is preferably carried out with sodium iodide in a suitable solvent, e.g. tetrahydrofuran or acetone. Preferably the reaction is carried out at a temperature from 20°C to the boiling point of the solvent for from 2 hours to 7 days.

The protective groups of the glycoside moiety, if present, may be removed according to the methods described in Ref. 1. If desired, the group R' may be removed by hydrolysis with base such as, for example, 0.5M - 2M sodium hydroxide, lithium hydroxide or potassium hydroxide in water, methanol, ethanol, or aqueous tetrahydrofuran. If R' is benzyl, it may be removed by catalytic hydrogenation in the presence of a catalyst, such as palladium on charcoal.

The suitably protected glycosides required as starting materials for the first step of the synthesis may be prepared from the corresponding unprotected glycosides, which may be obtained according to known methods for the synthesis of such compounds as described, for example, in Houben-Weyl, Methoden der Organischen Chemie, Auflage 4, Band E14a, Teil 3, Acetale III, p. 761-816. The methods for the preparation of the suitably protected glycosides involve the judicious use of protective group strategy, as illustrated in Ref. 1. For example selective protection of the primary hydroxyl group at the 6-position if a hexose or at the 5-position if a pentose may be achieved with a group such as, for example, triphenylmethyl or *tert*-butyldimethylsilyl. Such compounds with protected primary hydroxyl groups may then be derivatized at the remaining groups, where appropriate, by choosing a suitable group, e.g. from the list of groups given above. Selective removal of the protective group at the 6-position if a hexose or at the 5-position if a pentose then affords the suitably protected glycosides.

B. In a modification of the first step of the procedure described above in A, a phosphonoformate which is monosubstituted at the phosphonate group with a glycoside moiety, which may if necessary be suitably protected, may be obtained directly without the intermediacy of the phosphonoformate which is disubstituted at the phosphonate group with a glycoside moiety, which may if necessary be suitably protected. This may be achieved by reacting an alkoxycarbonylphosphonic dihalide or an aryloxycarbonylphosphonic dihalide with a glycoside ProtGlycoside-OH, which may if necessary be suitably protected, with a free hydroxyl group at the 6-position if a hexose or at the 5-position if a pentose followed by aqueous hydrolysis according to the formula:



followed as under A above by deprotection, if necessary, of the glycoside moiety, if desired with concomitant or subsequent removal of R', to give a compound of the formula IVb, e.g. as a salt, which in the case where R_{18} is R_5 corresponds to a compound of the formula I.

ProtGlycoside-OH, Hal, R', R_5 and R_{18} each have the same meaning as given above in A.

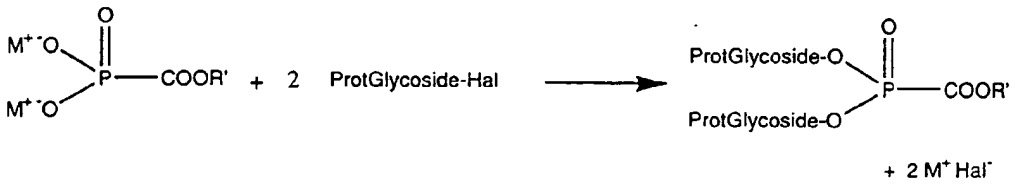
The first step of the synthesis is performed using more than one equivalent, preferably 1 to 2 equivalents, more preferably about 1.6 equivalents, of the alkoxycarbonylphosphonic dihalide or the aryloxycarbonylphosphonic dihalide per equivalent of glycoside, which may if necessary be suitably protected, in a solvent such as dichloromethane, dichloroethane, ethyl acetate or acetonitrile in the absence of base. Preferably the reaction is carried out at a temperature of -20°C to +5°C for 30 minutes to 2 hours followed by stirring at room temperature for 1 hour to 5 hours. Following removal of the solvent, the residue from the reaction mixture may be stirred vigorously for 5 to 30 minutes with a 1:1 mixture of water

and an organic solvent, for example, ethyl acetate or diethyl ether. The reaction may also be performed by using a glycoside, which may if necessary be suitably protected, in which an acid labile group such as a trisubstituted silyl ether group, for example a *tert*-butyldimethylsilyl ether group, is present at the 6-position if a hexose or at the 5-position if a pentose.

The protective groups of the glycoside moiety may be removed according to the methods described in Ref. 1, and the group R' may be removed, if desired, as described above in A.

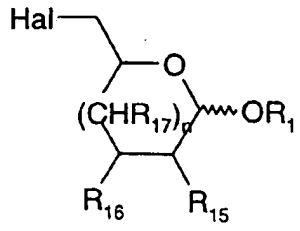
The modified procedure described in the first step of the above synthesis affords a convenient general method for the preparation of phosphonoformate diesters from e.g. alkoxycarbonylphosphonic dihalides or aryloxycarbonylphosphonic dihalides and alcohols or their trisubstituted silyl ethers without the need to first isolate a phosphonoformate triester.

C. Reacting a salt of an alkoxycarbonylphosphonate or an aryloxycarbonylphosphonate with a glycoside, which may if necessary be suitably protected with a halogen at the 6-position if a hexose or at the 5-position if a pentose, ProtGlycoside-Hal, according to the formula:



followed by selective removal of one of the protected glycoside groups as described above under A.

ProtGlycoside-Hal corresponds to a compound of the formula



VII

wherein n, Hal, R_1, R_{15}, R_{16}, R_{17}, and R' have the meanings given above in A.

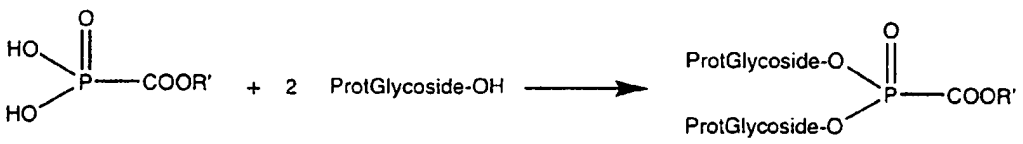
M^+ is a cation, e.g. Ag^+, Li^+, Na^+, K^+, Cs^+, Et_3NH^+ or $(i\text{-}Pr)_2NEtH^+$.

The first step of the synthesis is carried out in a solvent, for example, ethanol or dimethylformamide, at a temperature from 25°C to 100°C for 1 to 50 hours.

The second step of the synthesis is preferably carried out as above in A.

The protective groups of the glycoside moiety may be removed according to the methods described in Ref. 1, and the group R' may be removed, if desired, as described above in A.

D. Reacting an alkoxycarbonylphosphonic acid or an aryloxycarbonylphosphonic acid with a suitably protected glycoside ProtGlycoside-OH with a free hydroxyl group at the 6-position if a hexose or at the 5-position if a pentose, according to the formula:



followed by selective removal of one of the glycoside groups, which may be suitably protected,

and finally, if necessary, by deprotection of the glycoside moiety, if desired with removal of the group R', as above in A.

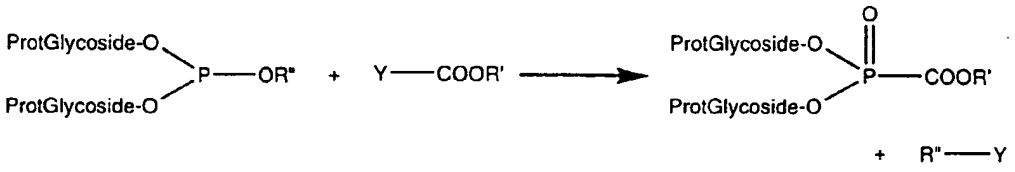
ProtGlycoside-OH, and R' are as above in A.

The first step of the synthesis may be performed through the intermediary of activating agents known *per se* for the phosphorylation of alcohols. Examples of such methods are described for example in Refs. 2 and 3.

The second step of the synthesis is preferably carried out as above in A.

The protective groups of the glycoside moiety may be removed according to the methods described in Ref. 1, and the group R' may be removed, if desired, as described above in A.

E. Reacting a suitably activated formate with suitably substituted phosphite triesters in which two of the ester groups are glycosides, which may be suitably protected if necessary, which are substituted at the 6-position if a hexose or at the 5-position if a pentose by the phosphite group according to the formula:



followed by selective removal of one of the glycoside groups, which may be suitably protected, and then, where necessary, subjecting the resulting compound to deprotection of the glycoside moiety, if desired with removal of the group R' as above in A.

ProtGlycoside-O- corresponds to a group derived from a compound of the formula V.

R' is as above in A.

R" is a C_{1-6}-alkyl, a C_{3-8}-cycloalkyl, a benzyl, an allyl or any phosphite esterifying group suitable for participation in an Arbuzov type reaction, and

Y is a leaving group suitable for Arbuzov type reactions, e.g. Cl, Br, I, sulphonate, carboxylate, or alkoxide.

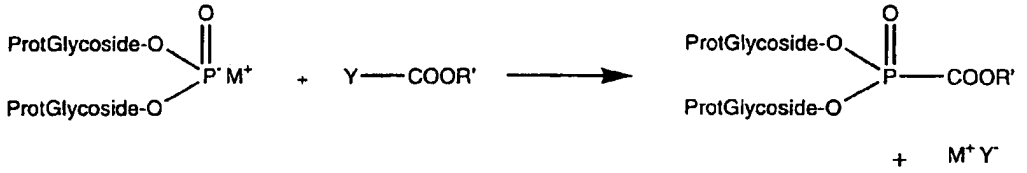
The first step of the synthesis may be performed at a temperature from 0°C to 150°C for 1 to 50 hours.

The second step of the synthesis is preferably carried out as above in A.

The protective groups of the glycoside moiety may be removed according to the methods described in Ref. 1, and the group R' may be removed, if desired, as described above in A.

The starting materials for the first step of the synthesis may be prepared by known methods commonly used for the synthesis of phosphite triesters and formates. Examples of methods used for the synthesis of phosphite triesters may be found in Houben-Weyl, Methoden der Organischen Chemie, Auflage 4, Band XII, Teil 2, Organische Phosphorverbindungen, p. 5-78. Examples of methods used for the synthesis of haloformate esters may be found in, or referred to in M. Matzner et al., Chem. Rev. 64 (1964) 645.

F. Reacting a suitably activated formate with a suitably substituted phosphite diester salt in which the ester groups are protected glycosides, which may be suitably protected if necessary, which are substituted at the 6-position if a hexose or at the 5-position if a pentose by the phosphite group according to the formula:



followed by selective removal of one of the protected glycoside groups as above in A.

ProtGlycoside-O- corresponds to a group derived from a compound of the formula V, and R' is as above in A. M^+ is a cation, preferably a metal ion, e.g. Li^+, Na^+ or K^+ and Y has the meaning given above.

The first step of the synthesis is preferably performed at 0°C to 100°C for 1 to 50 hours in a solvent for example toluene, ether or tetrahydrofuran.

The second step of the synthesis is preferably carried out as above in A.

The protective groups of the glycoside moiety and the group R' may be removed, if desired, as described above in A.

The phosphite diester salts are prepared by treating the phosphite diester with a suitable proton extracting compound, such as a metal alkoxide, suitably free from the alcohol, e.g. as lithium, sodium, or potassium methoxide, ethoxide, or *tert*-butoxide, or with a hydride e.g. sodium or potassium hydride, or with a base such as butyllithium.

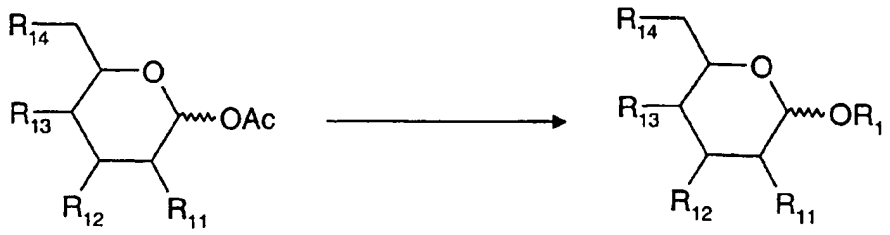
Experimental part

General description of the methods

^{1}H-, ^{13}C- and ^{31}P-NMR spectra were recorded on a Varian Unity 400 MHz spectrometer at 25 °C. The following reference signals were used: $CDCl_3$ δ 77.0 (^{13}C in $CDCl_3$); tetramethylsilane δ 0.00 (^{1}H in $CDCl_3$); 3-(trimethylsilyl)-propanesulfonic acid sodium salt δ 0.00 (^{1}H in D_2O); Me_2CO δ 31.00 (^{13}C in D_2O); the middle line of CD_3OD δ 49.0 (^{13}C in CD_3OD); the middle line of DMSO-d6 δ 39.5 (^{13}C in DMSO-d6); DMSO-d6 δ 2.5 (^{1}H in DMSO-d6). NMR-spectra recorded for all compounds were in agreement with the postulated structures and only selected data are reported. Thin layer chromatography (TLC) was performed on Merck DC-Fertigplatten® (Kieselgel 60 F_{254}, 0.25 mm) and on Merck DC-Alufolien® (Kieselgel 60 F_{254} 0.2 mm) and on Merck RP®-18 F_{254} (0.25 mm). Spots were visualized by UV and/or spraying with 8% aqueous sulfuric acid and charring. Merck Silica gel 60®(40-63 µm) was used for column chromatography in the flash mode. Merck LiChroprep® RP-18 (40-63 µm) was used for reversed phase chromatography. All solvents used were analytical grade (acetone and diethyl ether/Prolabo, dichloromethane/Fluka and the remaining from Merck) dried with 3Å (methanol) or 4Å molecular sieves, except tetrahydrofuran used for Birch reductions (Labscan of Anhydroscan grade).

Below is a detailed description of the synthesis of the intermediate and final compounds according to the present invention. The synthesis is performed stepwise to produce the compounds of the invention. The following abbreviations are used in the chemical formulas: Bn denotes a benzyl group, Bz denotes a benzoyl group, Tr denotes a triphenylmethyl group, Ac denotes an acetyl group, and Et denotes an ethyl group.

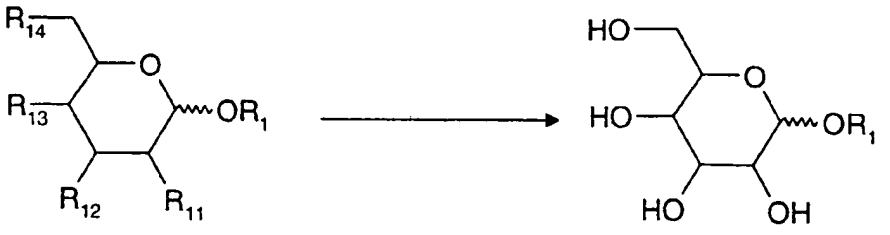
Glycosidations



In the figure above either R_{11}=R_{12}=R_{13}=R_{14} = OBn or R_{11}=R_{12}=R_{13}=R_{14} = OAc, and R_1 has the meaning stated above.

To a solution under argon, of the glycosyl donor (mixture of anomeric acetates) (5 mmoles) and the alcohol, (1.5 eq.) in CH_2Cl_2/Et_2O (1/2, 40 ml) was added activated 4 Å crushed molecular sieves. The mixture was stirred for 20 minutes, cooled to 0°C in an ice/water bath, and trimethylsilyl triflate (TMSOTf) (1.05 eq.) was added. The reaction was kept for 30 minutes at 0°C, and then allowed to warm up to room temperature. After 3 hours the reaction mixture was neutralized by addition of triethylamine (1.2 eq.) diluted with CH_2Cl_2 (40 ml), filtered, and evaporated. Flash chromatography of the residue gave the glycoside.

Preparation of the unprotected glycosides

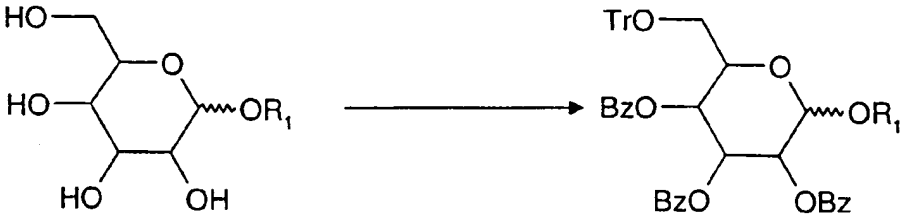


For deprotection of benzyl ethers by hydrogenolysis with palladium on charcoal, see e.g. McCloskey, C.M. in Wolfrom , M.L.(ed), *Adv Carbohydr. Chem.*, Academic Press Inc., New York, 12, 137-153, (1957).

For deprotection of benzyl ethers by Birch reduction, see e.g. Philips, K.D., Zemlicka, J. and Horowitz, J.P., Carbohydr. Res., 30 (1973) 281.

For deprotection of benzoyl esters by basic hydrolysis, see e.g. Conchie, J. and Levvy, G.A. in Whistler, R.L. and Wolfrom, M. L. (eds), *Methods in Carbohydrate Chemistry*, Academic Press Inc., New York and London, Vol. II, 345-347, (1963).

Tritylation and benzoylation

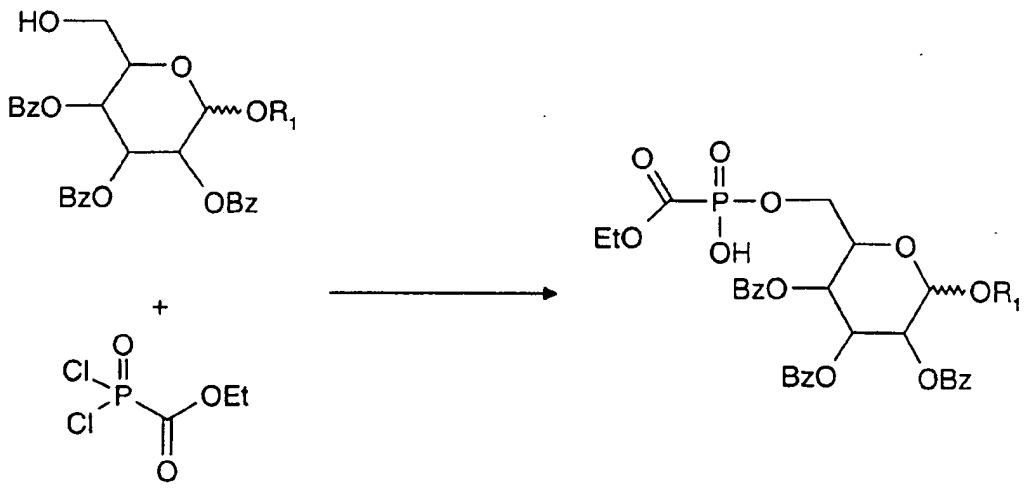


A solution of the glycoside (3 mmoles), triphenylmethyl chloride (1.1 eq.) and, a catalytic amount of 4-dimethylaminopyridine (DMAP) in 120 ml of pyridine was stirred overnight (14 hours) at 70° C. The solution was brought to room temperature, diluted with 60 ml of CH_2Cl_2 and benzoyl chloride (8 eq.) was added. After 12 hours at room temperature the reaction mixture was diluted with 60 ml of CH_2Cl_2 and washed with a saturated solution of $NaHCO_3$, then with H_2O and finally dried over $MgSO_4$. Filtration and evaporation (rotavapor, coevaporation of the traces of pyridine with toluene) followed by flash chromatography gave the title compounds.

Detritylation

To a solution of the trityl derivative (2 mmoles) in $CHCl_3$/MeOH (2/1, 90 ml) was added *para*-toluenesulfonic acid monohydrate to pH 1-2. After 3 hours the solution was diluted with 50 ml of CH_2Cl_2, washed with a saturated solution of $NaHCO_3$, then with H_2O and finally dried over $MgSO_4$. Filtration and evaporation followed by flash chromatography gave the title compounds.

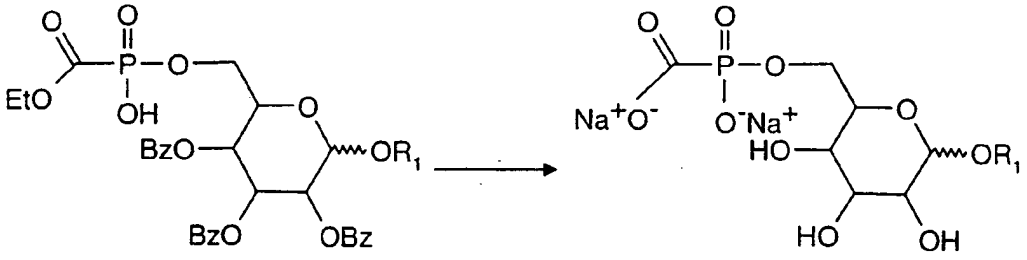
Preparation of diesters of phosphonoformic acid



A solution of the hydroxy compound (1 mmol) in dry CH_2Cl_2 (20 ml) was added dropwise to an ice cold solution of the ethoxycarbonylphosphonic dichloride (1.6 mmol) in dry CH_2Cl_2 (15

ml). The reaction was stirred at 0°C for an hour, and then for 3 hours at room temperature. The solvent was removed under reduced pressure, dried in high vacuum for 5 min., and redissolved in AcOEt (20 ml). 20 ml of H_2O were added and the two phases were vigorously stirred for 10 min. (emulsion). The organic phase was separated, and washed with H_2O. The aqueous phases were extracted twice with AcOEt (5% of MeOH was added when the phases separation was difficult). The combined organic phases were dried ($MgSO_4$), and evaporated. Flash chromatography of the residue gave the diesters.

Preparation of monoesters of phosphonoformic acid



The diester of foscarnet (1 mmol) was suspended in H_2O (25 ml) at room temperature. A 0.4 M solution of NaOH (25 ml) was added (insoluble product stuck to the walls of the flask was washed down with THF (10 ml)). The suspension was left 3 hours at room temperature., brought to pH 5-5.3 by addition of cation exchange resin (Dowex® 50W-X8 (H) standard grade, paricle size 0.39-1.00 mm), filtered, and the solvent was removed under reduced pressure (10 mm Hg, 30° C). If the solution could not be concentrated by drying in a rotavapor (due to rapid formation of a foam), the THF was removed by a continuous current of air overnight. The residue was purified by reverse phase chromatography, gradient: H_2O/MeOH 1/0 to 1/4). The fractions containing the monoester were collected, the MeOH evaporated (rotavapor, 20°C) and lyophilisation gave the title compounds.

The invention is further illustrated by the following non-limiting examples according to the procedures described above.

Examples of glycosidations according to the procedure described above under "Glycosidations":

Example 1

***n*-Octadecyl 2,3,4,6-tetra-O-benzyl–α–D-glucopyranoside:**

3.240 g of acetyl 2,3,4,6-tetra-O-benzyl-D -glucopyranoside (5.56 mmoles) and octadecanol gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/11) 3.097 g (71%) of the title compound.

R_f = 0.46 (AcOEt/petroleum ether 40°-60° C : 1/5).

^{1}H-NMR ($CDCl_3$): 7.37-7.12 (m, 20 H-arom.); 5.01-4.44 (m, 9H); 3.99 (t, J= 9.2 Hz); 3.76-3.40 (m, 7H); 1.62-1.58 (m, 2H); 1.32-1.19 (m, 30H); o.86 (t, J= 6.7Hz, 3H).

^{13}C -NMR ($CDCl_3$): 139.0-126.7 (C arom.); 96.9 (C(1)); 82.1; 80.1; 77.8; 75.6; 75.0; 73.4; 73.1; 70.1; 68.5; 68.2; 31.8-14.0 (C alkyl).

Example 2

***cis*-9-Octadecen-1-yl 2,3,4,6-tetra-O-benzyl–α–D-glucopyranoside:**

4 g of acetyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside (6.865 mmoles) and *cis*-9-octadecen-1-ol gave after flash chromatography 3 times (eluent AcOEt/petroleum ether 40°-60° C : 1/11) 3.719 g (68%) of the title compound.

R_f = 0.33 (AcOEt/petroleum ether 40°-60° C : 1/8).

^{1}H-NMR ($CDCl_3$): 7.36-7.12 (m, 20 H-arom.); 5.36-5.34 (m, 2H); 4.99 (d, J= 10.9 Hz); 4.84-4.44 (m, 8H); 3.99 (t, J= 9.2 Hz); 3.80-3.59 (m, 5H); 3.56 (dd, J= 9.6, 3.6 Hz, H-C(2)); 3.42

(dt, J= 9.8, 6.7 Hz); 2.03-1.99 (m,4H); 1.64-1.60 (m, 2H); 1.29-1.26 (m, 22H); 0.88 (t, J= 6.6 Hz, 3H).

^{13}C -NMR ($CDCl_3$): 138.9-137.9 (4C arom.); 129.-127.4 (C arom., 2C olef.); 96.8 (C(1)); 82.1; 80.1; 77.7; 75.6; 75.0; 73.4; 73.0; 70.0; 68.5; 68.2; 31.8-14.1 (C alkyl).

Example 3

***trans*-9-Octadecen-1-yl 2,3,4,6-tetra-O-benzyl–α–D-glucopyranoside:**

4 g of acetyl 2,3,4,6-tetra-O-benzyl-D-glucopyranoside (6.865 mmoles) and *trans*-9-octadecen-1-ol gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/11) 3.3 g (61%) of the title compound.

R_f = 0.30 (AcOEt/petroleum ether 40°-60° C : 1/10).

^{1}H-NMR ($CDCl_3$): 7.36-7.12 (m, 20 H-arom.); 5.39-5.37 (m, 2H); 4.99 (d, J= 11 Hz); 4.84-4.44 (m, 8H); 4.00 (t, J= 9.2 Hz); 3.80-3.59 (m, 5H); 3.56 (dd, J= 9.6, 3.6 Hz, H-C(2)); 3.42 (dt, J= 9.7, 6.7 Hz); 1.98-1.94 (m, 4H); 1.64-1.59 (m, 2H); 1.35-1.26 (m, 22H); 0.88 (t, J= 6.8 Hz, 3H).

^{13}C -NMR ($CDCl_3$): 138.9-137.9 (4C arom.); 130.3-127.4 (C arom., 2C olef.); 96.8 (C(1)); 82.0; 80.1; 77.7; 75.5; 74.9; 73.4; 73.0; 70.0; 68.5; 68.1; 32.5-14.0 (C alkyl).

Example 4

Eicosyl 2,3,4,6-tetra-O-acetyl–β–D-galactopyranoside:

3.5 g of 1,2,3,4,6-penta-O-acetyl-β-D-galactopyranoside (8.967 mmoles, purchased from Senn Chemicals AG) and eicosanol gave after a reaction time of 15 h, work up and flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/4) 1.45 g (26%) of the title compound.

R_f = 0.24 (AcOEt/petroleum ether 40°-60° C : 1/4).

^{1}H-NMR ($CDCl_3$): 5.39 (*br*.d, J= 2.6Hz, H-C(4)); 5.21 (dd, J= 9.4, 7.9 Hz, H-C(2)); 5.02 (dd, J= 10.4, 3.4 Hz, H-C(3)); 4.46 (d, J= 7.9 Hz, H-C(1)); 4.21-4.11 (m, 2H)); 3.92-3.86 (m, 2H);

3.47 (dt, J= 9.6, 6.9 Hz); 2.15, 2.05, 2.04, 1.98 (4s, 4 x 3H, Ac); 1.60-1.55 (m, 2H); 1.33-1.16 (m, 34H); 0.88 (t, J= 6.8 Hz, 3H).

^{13}C -NMR ($CDCl_3$): 170.3-169.2 (4 CO); 101.3 (C(1)); 70.9; 70.5; 70.2; 68.9; 67.0; 61.2; 31.9-14.0 (C alkyl and acetyl).

Examples of preparation of the unprotected glycosides (see the references given above under "Preparation of the unprotected glycosides"):

Example 5

***n*-Octadecyl α-D-glucopyranoside:**

A suspension of 1.28 g of *n*-octadecyl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside (1.615 mmoles) and 250 mg of 10% Pd/C in AcOEt/EtOH (1/1, 30 ml) was shaken 3 hours under an atmosphere of 3 bars of H_2 to give the title compound. The reaction mixture was filtered, and washed twice with 40 ml of AcOEt/MeOH/H_2O (7/2/1). The combined filtrates were evaporated, dried (high vacuum, 594 mg, 85%) and directly used in the next reaction step without further purification.

R_f = 0.19 (AcOEt/MeOH: 5/1).

Example 6

***cis*-9-Octadecen-1-yl α-D-glucopyranoside:**

A solution 2.184 g of *cis*-9-octadecen-1-yl 2,3,4,6-tetra-O-benzyl-α-D-glucopyranoside (2.76 mmoles) in THF (15 ml) was added dropwise over a period of 30 minutes to a solution of 1.01 g of sodium (43.9 mmoles) in 200 ml of liquid ammonia. The mixture was left stirring at -35°C. After 5 hours, MeOH (20 ml) and 2.34 g of NH_4Cl were added and the reaction mixture was left to warm up to room temperature. The ammonia was removed by a continuous current

of air overnight. The solid residue was suspended in AcOEt/MeOH (3/1, 100 ml) and filtered. Concentration of the filtrate, followed by flash chromatography (AcOEt/MeOH: 10/1) gave 642 mg (54 %) of *cis*-9-octadecen-1-yl α-D-glucopyranoside.

R_f = 0.23 (AcOEt/MeOH: 10/1).

^{1}H-NMR (CD_3OD, (ref. 3.24 ppm)): 5.29-5.26 (m, 2H olef.); 4.70 (d, J= 3.8 Hz, H-C(1)); 3.72 (dd, J= 11.8, 2.3 Hz, H-C(6)); 3.66 (dt, J= 9.6, 6.9 Hz); 3.61 (dd, J= 11.8, 5.5 Hz, H-C(6)); 3.56 (t, J= 9.3 Hz); 3.50 (ddd, J= 9.7, 5.4, 2.3 Hz, H-C(5)); 3.37 (dt, J= 9.6, 6.6 Hz); 3.31 (dd, J= 9.6, 3.8 Hz, H-C(2)); 3.22 (t, J= 9.5 Hz); 1.97-1.94 (m ,4H); 1.59-1.54 (m, 2H); 1.33-1.17 (m, 22H); 0.89 (t, J= 6.8 Hz, 3H).

^{13}C -NMR (CD_3OD): 130.8 (2C olef.); 100.1 (C(1)); 75.1; 73.6 (2C); 71.8; 69.1; 62.7; 33.1-13.4 (C alkyl).

Example 7

***trans*-9-Octadecen-1-yl α-D-glucopyranoside:**

A solution 2.4 g of *trans*-9-octadecen-1-yl 2,3,4,6-tetra-O-benzyl–α–D-glucopyranoside (3.03 mmoles) in THF (15 ml) was added dropwise over a period of 30 minutes to a solution of 1.4 g of sodium (60 mmoles) in 200 ml of liquid ammonia. The mixture was left stirring at -35°C. After 5 hours, MeOH (20 ml) and 3.21 g of NH_4Cl were added and the reaction mixture was left to warm up to room temperature. The ammonia was removed by a continuous current of air overnight. The solid residue was suspended in AcOEt/MeOH (3/1, 100 ml) and filtered. Concentration of the filtrate and followed by flash chromatography (AcOEt/MeOH: 10/1) gave 728 mg (56%) of *trans*-9-octadecen-1-yl α -D-glucopyranoside.

R_f = 0.23 (AcOEt/MeOH: 10/1).

^{1}H-NMR ($CDCl_3/CD_3OD$: 2/1(ref. 3.35 ppm)): 5.39 (m, 2H olef.); 4.82 (d, J= 3.8 Hz, H-C(1)); 3.79-3.65 (m, 4H); 3.59 (dt, J= 9.7, 3.6 Hz); 3.48-3.38 (m, 3H); 1.98-1.95 (m ,4H); 1.65-1.61 (m, 2H); 1.34-1.27 (m, 22H); 0.89 (t, J= 6.9 Hz, 3H).

^{13}C -NMR ($CDCl_3$/ CD_3OD: 2/1, (ref. 77.0 ppm)): 130.0, 129.9 (2C olef.); 98.2 (C(1)); 73.6; 71.8; 71.3; 69.9; 69.1; 67.8; 61.1; 32.1-13.4 (C alkyl).

Example 8

Eicosyl β-D-galactopyranoside:

To a solution of 1.38 g of eicosyl 2,3,4,6-tetra-O-acetyl-β-D-galactopyranoside (2.194 mmoles) in MeOH (50 ml) was added a solution of MeO^-Na^+ in MeOH (0.01 M, 20 ml). After 3 hours the reaction mixture was neutralized by addition of cation exchanger resin (Dowex 50W-X8 (H) standare grade, particle size 0.39-1.00 mm) and diluted by $CHCl_3$ (100 ml). Filtration, evaporation gave 990 mg of a residue (98 %) consisting of the title compound, which was directly used in the next reaction step without further purification.

R_f = 0.21 (AcOEt/MeOH: 5/1).

Examples of tritylation and benzoylation according to the procedure described above under "Tritylation and benzoylation":

Example 9

***n*-Octadecyl 2,3,4-tri-O-benzoyl-6-O-trityl–α–D-glucopyranoside:**

660 mg of *n*-octadecyl α-D-glucopyranoside (1.37 mmoles) gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/8) 965 mg (72%) of the title compound.

R_f = 0.25 (AcOEt/petroleum ether 40°-60° C : 1/8).

^{1}H-NMR ($CDCl_3$): 8.01-7.07 (m, 30 H-arom.); 6.10 (t, J= 9.8 Hz); 5.56 (t, J= 10 Hz); 5.40 (d, J= 3.7 Hz, H-C(1)); 5.30 (dd, J= 10.1, 3.8 Hz, H-C(2)); 4.26 (dt, J= 10, 3.9 Hz, H-C(5)); 3.88 (dt, J= 9.7, 6.4 Hz); 3.51(dt, J= 9.7, 6.6 Hz); 3.29-3.28 (m, 2H, H-C(6)); 1.68-1.61 (m, 2H); 1.35-1.18 (m, 30H); 0.85 (t,3H).

Example 10

***cis*-9-Octadecen-1-yl 2,3,4-tri-O-benzoyl-6-O-trityl–α–D-glucopyranoside:**

642 mg of *cis*-9-octadecen-1-yl α-D-glucopyranoside (1.5 mmoles) gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/9) 1.148 mg (78%) of the title compound.

R_f = 0.23 (AcOEt/petroleum ether 40°-60° C : 1/9).

^{1}H-NMR ($CDCl_3$): 8.01-7.07 (m, 30 H-arom.); 6.11 (t, J= 9.8 Hz); 5.56 (t, J= 9.9 Hz); 5.40 (d, J= 3.8 Hz, H-C(1)); 5.37-5.33 (m, 2H); 5.30 (dd, J= 10.1, 3.8 Hz, H-C(2));4.26 (dt, J= 10.1, 4 Hz, H-C(5)); 3.88 (dt, J= 9.8, 6.4 Hz); 3.52 (dt, J= 9.7, 6.6 Hz); 3.29-3.28 (m, 2H, H-C(6)); 2.02-1.96 (m, 4H); 1.66-1.60 (m, 2H); 1.35-1.17 (m, 22H); 0.86 (t, J= 6.7Hz, 3H).

^{13}C -NMR ($CDCl_3$): 165.8-164.9 (3 C, CO); 146-126.8 (C arom.); 95.7 (C(1)); 86.6; 72.3; 71; 69.7; 69.3; 68.4; 62.6; 31.8-14 (C alkyl).

Example 11

***trans*-9-Octadecen-1-yl 2,3,4-tri-O-benzoyl-6-O-trityl–α–D-glucopyranoside:**

728 mg of *trans*-9-octadecen-1-yl α-D-glucopyranoside (1.69 mmoles) gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/9) 1.590 mg (95 %) of the title compound.

R_f = 0.23 (AcOEt/petroleum ether 40°-60° C : 1/9).

^{1}H-NMR ($CDCl_3$): 8.01-7.07 (m, 30 H-arom.); 6.11 (t, J= 9.9 Hz); 5.56 (t, J= 9.9 Hz); 5.40-5.37 (m, 3 H); 5.32 (dd, J= 10.1, 3.7 Hz, H-C(2)); 4.26 (dt, J= 10.1, 4 Hz, H-C(5)); 3.88 (dt, J= 9.8, 6.5 Hz); 3.51 (dt, J= 9.7, 6.6 Hz); 3.29-3.28 (m, 2H, H-C(6)); 1.99-1.91 (m, 4H); 1.66-1.60 (m, 2H); 1.35-1.17 (m, 22H); 0.87 (t, J= 6.8 Hz, 3H).

^{13}C -NMR ($CDCl_3$): 165.8-164.9 (3 C, CO); 146-126.8 (C arom.); 95.7 (C(1)); 86.6; 72.3; 71; 69.7; 69.3; 68.4; 62.6; 32.6-14.1 (C alkyl).

Example 12

n-Dodecyl 2,3,4-tri-O-benzoyl-6-O-trityl-α-D-glucopyranoside:

1 g of *n*-dodecyl α-D-glucopyranoside (3.52 mmoles) gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/8) 2.52 g (79 %) of the title compound.

R_f = 0.21 (AcOEt/petroleum ether 40°-60° C : 1/9).

^{1}H-NMR ($CDCl_3$): 8.15-7.07 (m, 30 H-arom.); 6.12 (t, J= 9.7 Hz); 5.57 (t, J= 9.9 Hz); 5.40 (d, J= 3.6 Hz, H-C(1)); 5.32 (dd, J= 10.1, 3.6 Hz, H-C(2)); 4.27 (dt, J= 10.1, 3.9 Hz, H-C(5)); 3.88 (dt, J= 9.8, 6.5 Hz); 3.52 (dt, J= 9.8, 6.8 Hz); 3.30-3.29 (m, 2H, H-C(6)); 1.67-1.63 (m, 2H); 1.38-1.17 (m, 18H); 0.88 (t, J= 6.8 Hz, 3H).

^{13}C -NMR ($CDCl_3$): 165.8-164.9 (3 C, CO); 143.6-126.8 (C arom.); 95.7 (C(1)); 86.6; 72.3; 71.0; 69.7; 69.3; 68.4; 62.6; 31.9-14.1 (C alkyl).

Example 13

Eicosyl 2,3,4-tri-O-benzoyl-6-O-trityl-β-D-galactopyranoside:

990 mg of eicosyl β-D-galactopyranoside (2.15 mmoles) gave after flash chromatography (gradient AcOEt/petroleum ether 40°-60° C : 1/12 to 1/8) 1.98 g (84 %) of the title compound.

R_f = 0.19 (AcOEt/petroleum ether 40°-60° C : 1/10).

^{1}H-NMR ($CDCl_3$): 7.95-7.09 (m, 30H); 6.06 (d, J= 3.1 Hz, H-C(4)); 5.67 (dd, J= 10.4, 7.6 Hz, H-C(2)); 5.61 (dd, J= 10.4, 3.2 Hz, H-C(3)); 4.72 (d, J= 7.5 Hz, H-C(1)); 4.12-3.90 (m, 3H); 3.53-3.47 (m, 2H); 3.29 (dd appearing as t, J= 8.5 Hz); 1.56-1.47 (m, 2H); 1.35-1.01 (m, 34H); 0.87 (m, 3H).

^{13}C -NMR ($CDCl_3$): 165.2-165.1 (3 C, CO); 143.3-126.9 (C arom.); 101.6 (C(1)); 86.9; 72.5; 71.9; 70.3; 70.0; 68.1; 61.0; 31.9-14.1 (C alkyl).

Examples of detritylation according to the procedure described above under "Detritylation":

Example 14

***n*-Octadecyl 2,3,4-tri-O-benzoyl–α–D-glucopyranoside:**

1.29 g of *n*-octadecyl 2,3,4-tri-O-benzoyl-6-O-trityl–α–D-glucopyranoside (1.3 mmoles) gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/4) 730 mg (75%) of the title compound.

R_f = 0.25 (AcOEt/petroleum ether 40°-60° C : 1/4).

^{1}H-NMR ($CDCl_3$): 8.01-7.24 (m, 15 H-arom.); 6.26 (t, J= 9.8 Hz); 5.53 (t, J= 9.9 Hz); 5.39 (d, J= 3.8 Hz, H-C(1)); 5.31 (dd, J= 10.1, 3.8 Hz, H-C(2)); 4.11 (m, H-C(5)); 3.83-3.73 (m, 3H); 3.48 (dt, J= 9.9, 6.6 Hz); 2.85 (dd, J= 7, 5.8 Hz, HO-C(6)); 1.62-1.56 (m, 2H); 1.31-1.14 (m, 30H); 0.88 (t, J= 6.9 Hz, 3H).

^{13}C -NMR ($CDCl_3$): 166.2-165.6 (3 C, CO); 133.5-126.8 (C arom.); 95.9 (C(1)); 72.0; 70.3; 69.8; 69.6; 68.7; 61.0; 31.8-14.1 (C alkyl).

Example 15

***cis*-9-Octadecen-1-yl 2,3,4-tri-O-benzoyl–α–D-glucopyranoside:**

1.08 g of *cis*-9-octadecen-1-yl 2,3,4-tri-O-benzoyl-6-O-trityl–α–D-glucopyranoside (1.1 mmoles) gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/3.5) 590 mg (72%) of the title compound.

R_f = 0.23 (AcOEt/petroleum ether 40°-60° C : 1/3.5).

^{1}H-NMR ($CDCl_3$): 8.00-7.24 (m, 15 H-arom.); 6.26 (t, J= 9.9 Hz); 5.53 (t, J= 9.8 Hz); 5.39 (d, J= 3.7 Hz, H-C(1)); 5.36-5.33 (m, 2H); 5.31 (dd, J= 10.1, 3.7 Hz, H-C(2)); 4.11-4.08 (m, H-C(5)); 3.84-3.72 (m, 3H); 3.48 (dt, J= 9.9, 6.6 Hz); 2.84 (*br*.s, HO-C(6)); 2.02-1.96 (m, 4H); 1.64-1.56 (m, 2H); 1.26-1.14 (m, 22H); 0.87 (t, J= 6.8 Hz, 3H).

^{13}C -NMR ($CDCl_3$): 166.2-165.6 (3 C, CO); 133.5-128.2 (C arom.); 95.9 (C(1)); 72.0; 70.3; 69.8; 69.6; 68.7; 61.0; 31.8-14.0 (C alkyl).

Example 16

***trans*-Octadecen-1-yl 2,3,4-tri-O-benzoyl–α–D-glucopyranoside:**

1.653 g of *trans*-octadecen-1-yl 2,3,4-tri-O-benzoyl-6-O-trityl–α–D-glucopyranoside (1.68 mmoles) gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/3.5) 919 mg (74%) of the title compound.

R_f = 0.23 (AcOEt/petroleum ether 40°-60° C : 1/3.5).

^{1}H-NMR ($CDCl_3$): 8.00-7.25 (m, 15 H-arom.); 6.25 (t, J= 9.9 Hz); 5.51 (t, J= 9.8 Hz); 5.38-5.37 (m, 3H); 5.30 (dd, J= 10.1, 3.7 Hz, H-C(2)); 4.09 (*br*.d, J= 9.8 Hz, H-C(5)); 3.84-3.73 (m, 3H); 3.47 (dt, J= 9.8, 6.6 Hz); 2.80 (*br*.s, HO-C(6)); 1.99-1.91 (m, 4H); 1.64-1.54 (m, 2H); 1.38-1.14 (m, 22H); 0.88 (m, 3H).

^{13}C -NMR ($CDCl_3$): 166.3-165.7 (3 C, CO); 133.6-128.2 (C arom.); 95.9 (C(1)); 72.1; 70.3; 69.8; 69.6; 68.7; 61.1; 32.5-14.0 (C alkyl).

Example 17

***n*-Tetradecyl 2,3,4-tri-O-benzoyl–α–D-glucopyranoside:**

The 6-O-trityl derivative of the title compound was prepared as follows. 2,3,4,6-Tetra-O-benzyl-α-D-glucopyranosyl chloride (5g, 8.9 mmol), obtained by treatment of commercially available 2,3,4,6-tetra-O-benzyl-α-D-glucopyranose with *N*,*N*-dimethylformamide and oxalyl chloride in dichloromethane, *n*-tetradecanol (13.4 mmol) and tetrabutylammonium bromide (13.4 mmol) were dissolved in CH_2Cl_2 containing molecular sieves (4Å) and stirred at room temperature for three days. TLC (toluene: EtOAc 6:1) indicated that only about half of the starting material was consumed. Silver trifluoromethanesulfonate (8.9 mmol) dissolved in toluene was therefore added. After 1 h triethylamine (26.8 mmol) was added to the reaction mixture, which then was applied directly on top of a silica gel column and eluted to give the α- and the β-anomer in a mixture. The mixture was dissolved in EtOAc and hydrogenolyzed over palladium on

charcoal at 60 psi in a Parr apparatus overnight. The catalyst was filtered off and the filtrate concentrated. Flash chromatography was performed to separate the anomeric mixture, giving the anomers in a ratio of 3:1 (α:β). The β-anomer was used in Example 18. The residue was dissolved in pyridine and triphenylmethyl chloride (9.8 mmol) and dimethylaminopyridine (catalytic amount) was added. The mixture was heated at 55 °C and stirred for three days, then diluted with $CHCl_3$ and the organic phase washed with $Na_2S_2O_3$ (twice), $NaHCO_3$ (3 times) and water (twice), then dried (Na_2SO_4) and concentrated. The residue was dissolved in pyridine and cooled in an ice-bath. Benzoyl chloride (44.5 mmol) was added dropwise. The mixture was allowed to attain room temperature and stirred for an additional hour whereafter ice was added to the mixture. After another hour the mixture was diluted with toluene and the organic phase was separated and washed with water, $NaHCO_3$ and water, dried (Na_2SO_4) and concentrated. The residue was purified on a silica gel column to give *n*-tetradecyl 2,3,4-tri-O-benzoyl-6-O-trityl-α-D-glucopyranoside.

Detritylation of *n*-tetradecyl 2,3,4-tri-O-benzoyl-6-O-trityl-α-D-glucopyranoside was performed with stirring for 1 hour only, giving after flash chromatography 300 mg (48%) of the title compound.

^{13}C -NMR ($CDCl_3$ (ref.77.17 ppm), JEOL GX-270): 166.2-165.7 (3 C, CO); 133.5-128.2 (C arom.); 95.9 (C(1)); 72.1; 70.5; 69.9; 69.6; 68.7; 61.1; 31.9-14.1 (C alkyl).

Example 18

n-Tetradecyl 2,3,4-tri-O-benzoyl–β–D-glucopyranoside:

In order to prepare the 6-O-trityl derivative of the title compound, *n*-tetradecyl β-D-glucopyranoside (produced as in Example 17) was dissolved in pyridine and triphenylmethyl chloride (9.8 mmol) and dimethylaminopyridine (catalytic amount) were added. The mixture was heated at 55 °C and stirred for three days, then diluted with $CHCl_3$ and the organic phase washed with $Na_2S_2O_3$ (twice), $NaHCO_3$ (3 times) and water (twice), then dried (Na_2SO_4) and concentrated. The residue was dissolved in pyridine and cooled in an ice-bath. Benzoyl chloride (44.5 mmol) was added dropwise. The mixture was allowed to attain room temperature and stirred for an additional hour whereafter ice was added to the mixture. After another hour the mixture was diluted with toluene and the organic phase was separated and washed with water, $NaHCO_3$ and water, dried (Na_2SO_4) and

concentrated. The residue was purified on a silica gel column to give *n*-tetradecyl 2,3,4-tri-O-benzoyl-6-O-trityl-β-D-glucopyranoside.

Detritylation of *n*-tetradecyl 2,3,4-tri-O-benzoyl-6-O-trityl-β-D-glucopyranoside was performed with stirring for 1 hour only, giving after flash chromatography 56 mg (9%) of the title compound.

^{13}C -NMR ($CDCl_3$ (ref. 77.17 ppm), JEOL GX-270): 166.2-165.7 (3 C, CO); 133.5-128.2 (C arom.); 95.9 (C(1)); 72.1; 70.5; 69.9; 69.6; 68.7; 61.1; 31.9-14.1 (C alkyl).

Example 19

Dodecyl 2,3,4-tri-O-benzoyl–α–D-glucopyranoside:

2.8 g of *n*-dodecyl 2,3,4-tri-O-benzoyl-6-O-trityl–α–D-glucopyranoside (3.1 mmoles) gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/3.5) 1.564 g (76%) of the title compound.

R_f = 0.17 (AcOEt/petroleum ether 40°-60° C : 1/4).

^1H-NMR ($CDCl_3$): 8.01-7.25 (m, 15 H-arom.); 6.26 (t, J= 9.9 Hz); 5.52 (t, J= 9.8 Hz); 5.38 (d, J= 3.8 Hz, H-C(1)); 5.30 (dd, J= 10.1, 3.8 Hz, H-C(2)); 4.10 (ddd, J= 9.8, 3.5, 2.1 Hz, H-C(5)); 3.82-3.73 (m, 3H); 3.48 (dt, J= 9.9, 6.6 Hz); 2.81 (*br.*s, HO-C(6)); 1.62-1.58 (m, 2H); 1.31-1.15 (m, 18H); 0.88 (t, J= 6.9 Hz, 3H).

^{13}C -NMR ($CDCl_3$): 166.3-165.7 (3 C, CO); 133.5-128.2 (C arom.); 95.9 (C(1)); 72.0; 70.3; 69.8; 69.6; 68.7; 61.0; 31.8-14.0 (C alkyl).

Example 20

Eicosyl 2,3,4-tri-O-benzoyl–β–D-galactopyranoside:

1.5 g of eicosyl 2,3,4-tri-O-benzoyl-6-O-trityl–α–D-galactopyranoside (1.48 mmoles) gave after flash chromatography (eluent AcOEt/petroleum ether 40°-60° C : 1/3) 901 mg (79%) of the title compound.

R_f = 0.24 (AcOEt/petroleum ether 40°-60° C : 1/3).

^{1}H-NMR ($CDCl_3$): 8,15-7.23 (m, 15H); 5.84 (dd, J= 10.4, 7.9 Hz, H-C(2)); 5.82 (d, J= 3.3 Hz, H-C(4)); 5.59 (dd, J= 10.4, 3.3 Hz, H-C(3)); 4.79 (d, J= 7.9 Hz, H-C(1)); 4.03 (t, J= 6.9 Hz); 3.96 (dt, J= 9.6, 6.1 Hz); 3.84 (dt, J= 11.9, 7.0 Hz, H-C(6)); 3.66 (dt, J= 11.9, 6.9 Hz, H-C(6)); 3.56 (dt, J= 9.6, 6.8 Hz); 2.65 (t, J= 7.2 Hz, HO-C(6)); 1.63-1.50 (m, 2H); 1.39-1.00 (m, 34H); 0.88 (dd, J= 6.7, 6.1 Hz, 3H).

^{13}C -NMR ($CDCl_3$): 166.9-165.3 (3 C, CO); 133.8-128.3 (C arom.); 101.8 (C(1)); 74.0; 71.8; 70.6; 70.0; 69.1; 60.6; 31.9-14.1 (C alkyl).

Examples of preparation of diesters of phosphonoformic acid according to the procedure described above under "Preparation of diesters of phosphonoformic acid"

Example 21

***n*-Octadecyl 2,3,4-tri-O-benzoyl-α-D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate:** 700 mg of octadecyl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside (0.94 mmoles) gave after flash chromatography (gradient AcOEt/MeOH : 5/1 to AcOEt/MeOH/H_2O: 8/1.5/0.5) 580 mg (70%) of the title compound.

R_f = 0.31 (AcOEt/MeOH : 5/1).

^{1}H-NMR (DMSO-d6): 7.96-7.47 (m, 15 H-arom.); 6.03 (t, J= 9.7 Hz); 5.59 (t, J= 9.8 Hz); 5.39 (d, J= 3.4 Hz, H-C(1)); 5.34 (dd, J= 10.1, 3.4 Hz, H-C(2)); 4.37-4.33 (m, H-C(5)); 4.09-3.86 (m, 5H); 3.55 (m, 1H); 1.66-1.62 (m, 2H); 1.35-1.23 (m, 30H); 1.14 (t, J= 7.1 Hz, 3H); 0.92 (t, J= 6.7 Hz, 3H).

^{13}C -NMR (DMSO-d6): 174 (d, J_{CO-P} = 249 Hz); 165.2-164.5 (3 C, CO); 133.7-128.6 (C arom.); 94.9 (C(1)); 71.4; 70.9; 69.0; 68.7 (d, J_{C-P} = 5.6 Hz); 67.5; 63.6 (d, J_{C-P} = 3.2 Hz); 58.4 (*br*.d); 31.3-13.9 (C alkyl).

Example 22

cis-9-Octadecen-1-yl 2,3,4-tri-O-benzoyl-α-D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate:

590 mg of _cis_-9-octadecen-1-yl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside (0.794 mmoles) gave after flash chromatography (gradient AcOEt/MeOH : 5/1 to AcOEt/MeOH/H_2O: 8/1.5/0.5) 600 mg (86%) of the title compound.

R_f = 0.23 (AcOEt/MeOH : 5/1).

^{1}H-NMR ($CDCl_3$/CD_3OD: 2/1, (ref. 3.36 ppm)): 7.96-7.26 (m, 15 H-arom.); 6.16 (t, J= 9.7 Hz); 5.64 (t, J= 9.8 Hz); 5.34-5.31 (m, 3H); 5.24 (dd, J= 10.3, 3.4 Hz, H-C(2)); 4.32-4.09 (m, 5H); 3.86-3.82 (m, 1H); 3.48-3.43 (m, 1H); 2.02-1.95 (m, 4H); 1.58-1.54 (m, 2H); 1.27-1.10 (m, 25H); 0.88 (m, 3H).

^{13}C -NMR ($CDCl_3$/CD_3OD: 2/1, (ref. 49.0 ppm)): 173.6 (d, J_{CO-P} = 250 Hz); 166.4-165.9 (3 C, CO); 133.9-128.6 (C arom.); 96.2 (C(1)); 72.4; 71.3; 69.5; 69.3 (d, J_{C-P} = 7.5 Hz); 69.1; 64.9 (d, J_{C-P} = 5.3 Hz); 61.3(d, J_{C-P} = 3.8 Hz); 32.2-14.1 (C alkyl).

Example 23

trans-9-Octadecen-1-yl 2,3,4-tri-O-benzoyl-α-D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate:

919 mg of _trans_-9-octadecen-1-yl 2,3,4-tri-O-benzoyl-α-D-glucopyranoside (1.237 mmoles) gave after flash chromatography (gradient AcOEt/MeOH : 5/1 to AcOEt/MeOH/H_2O: 8/1.5/0.5) 872 mg (80%) of the title compound.

R_f = 0.23 (AcOEt/MeOH : 5/1).

^{1}H-NMR ($CDCl_3$/ CD_3OD: 2/1, (ref. 3.35 ppm)): 7.97-7.27 (m, 15 H-arom.); 6.15 (t, J= 9.7 Hz); 5.63 (t, J= 9.8 Hz); 5.39-5.36 (m, 2H); 5.32 (d, J= 3.7 Hz, H-C(1)); 5.24 (dd, J= 10.1, 3.7 Hz, H-C(2)); 4.33-4.09 (m, 5H); 3.86 (dt, J= 9.8, 6.3 Hz); 3.47 (dt, J= 9.8, 6.1 Hz); 2.00-1.90 (m, 4H); 1.58-1.54 (m, 2H); 1.27-1.10 (m, 25H); 0.88 (t, J= 6.7 Hz, 3H).

^{13}C -NMR ($CDCl_3$/ CD_3OD: 2/1, (ref. 77.0 ppm)): 172.7 (d, J_{CO-P} = 250 Hz); 165.6-165.1 (3 C, CO); 133.1-127.8 (C arom.); 95.4 (C(1)); 71.6; 70.5; 68.6; 68.3 (d, J_{C-P} = 6.9 Hz); 68.2; 64.1 (d, J_{C-P} = 5.2 Hz); 60.4 (d, J_{C-P} = 3.8 Hz); 32.0-13.2 (C alkyl).

Example 24

***n*-Tetradecyl 2,3,4-tri-O-benzoyl–α–D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate:**

Deviation from the general procedure: Stirring at room temperature only one extra hour, and after extraction dried with Na_2SO_4. 1 g of *n*-tetradecyl 2,3,4-tri-O-benzoyl–α–D-glucopyranoside (1.45 mmoles) gave after flash chromatography (AcOEt/MeOH/H_2O: 10/1.5/0.5) 413 mg (34%) of the title compound.

R_f = 0.25 (AcOEt/MeOH/H_2O: 10/1.5/0.5).

^{1}H-NMR (DMSO-d6): 7.9-7.4 (m, 15 H-arom.); 5.92 (t, J= 9.8 Hz); 5.47 (t, J= 9.8 Hz); 5.29 (d, J= 3.6 Hz, H-C(1)); 5.25 (dd, J= 10.4, 3.6 Hz, H-C(2)); 1.14 (t); 0.92 (t).

^{13}C -NMR (DMSO-d6): 176.2 (d, J_{CO-P} = 232 Hz); 165.2-164.5 (3 C, CO); 133.8-128.5 (C arom.); 94.8 (C(1)); 71.4; 70.9; 69.0; 68.8 (d, J_{C-P} = 6.9 Hz); 67.5; 63.5 (d, J_{C-P} = 5.3 Hz); 58.2 (d, J_{C-P} = 3.0 Hz);); 31.3-13.9 (C alkyl).

Example 25

***n*-Tetradecyl 2,3,4-tri-O-benzoyl–β–D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate:**

Deviation from the general procedure: Stirring at room temperature only one extra hour, and after extraction dried with Na_2SO_4. 561 mg of tetradecyl 2,3,4-tri-O-benzoyl–β–D-glucopyranoside (0.81 mmoles) gave after flash chromatography (AcOEt/MeOH/H_2O: 10/1.5/0.5) 305 mg (45%) of the title compound.

R_f = 0.5 (AcOEt/MeOH/H_2O: 8/1.5/0.5).

^{1}H-NMR (DMSO-d6): 8.2-7.0 (m, 15 H-arom.); 5.92 (t, J= 9.6 Hz); 5.43 (t, J= 9.6 Hz); 5.27 (t, J= 9.6 Hz); 5.10 (d, J= 9.1, H-C(1)); 4.4-3.68 (m).

^{13}C -NMR (DMSO-d6): 165.0-164.5 (3 C, CO); 135.1-127.4 (C arom.); 99.5 (C(1)); 73.3; 72.1 (d, J_{C-P} = 6.9 Hz); 71.7; 69.0; 64.3; 59.6 (d, J_{C-P} = 3.8 Hz); 31.3-13.5 (C alkyl).

Example 26

***n*-Dodecyl 2,3,4-tri-O-benzoyl–α–D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate:**

1.3 g of *n*-dodecyl 2,3,4-tri-O-benzoyl–α–D-glucopyranoside (1.97 mmoles) gave after flash chromatography (gradient AcOEt/MeOH : 5/1 to AcOEt/MeOH/H_2O: 8/1.5/0.5) 1.345 mg (86%) of the title compound.

R_f = 0.20 (AcOEt/MeOH : 5/1).

^{1}H-NMR ($CDCl_3$/ CD_3OD: 2/1): 7.96-7.24 (m, 15 H-arom.); 6.18 (t, J= 9.8 Hz); 5.66 (t, J= 9.7 Hz); 5.34 (d, J= 3.5 Hz, H-C(1)); 5.26 (dd, J= 10.1, 3.5 Hz, H-C(2)); 4.33-4.11 (m, 5H); 3.86 (m, 1H); 3.47 (dt, J= 9.8, 6.7 Hz); 1.64-1.55 (m, 2H); 1.32-1.14 (m, 21H); 0.88 (t, J= 6.8 Hz, 3H).

^{13}C -NMR ($CDCl_3$/ CD_3OD: 2/1, (ref. 77.0 ppm)): 172.8 (d, J_{CO-P} = 251 Hz); 165.6-165.1 (3 C, CO); 133.1-127.8 (C arom.); 95.4 (C(1)); 71.6; 70.5; 68.7; 68.3 (d, J_{C-P} = 7.7 Hz); 68.2; 64.1 (d, J_{C-P} = 4.9 Hz); 60.4 (d, J_{C-P} = 3.8 Hz); 31.4-13.3 (C alkyl).

Example 27

Eicosyl 2,3,4-tri-O-benzoyl–β–D-galactopyranosid-6-yl (ethoxycarbonyl)phosphonate:

854 mg of eicosyl 2,3,4-tri-O-benzoyl–α–D-galactopyranoside (1.1 mmoles) gave after flash chromatography (gradient AcOEt/MeOH : 5/1 to AcOEt/MeOH/H_2O: 8/1.5/0.5) 803 mg (80%) of the title compound.

R_f = 0.25 (AcOEt/MeOH : 5/1).

^{1}H-NMR ($CDCl_3$/ CD_3OD: 2/1): 8.06-7.24 (m, 15 H-arom.); 5.96 (d, J= 3.2 Hz, H-C(4); 5.74 (dd, J= 10.2, 7.9 Hz, H-C(2)); 5.62 (dd, J= 10.4, 3.2 Hz, H-C(3)); 4.89 (d, J= 7.9 Hz, H-C(1));

4.34-3.96 (m, 6H); 3.62-3.56 (m, 1H); 1.56-1.49 (m, 2H); 1.32-1.00 (m, 37H); 0.88 (t, J= 6.7 Hz, 3H).

^{13}C -NMR ($CDCl_3$/ CD_3OD: 2/1, (ref. 77.0 ppm)): 172.7 (d, J_{CO-P} = 249 Hz); 165.7-165.3 (3 C, CO); 133.3-127.9 (C arom.); 101.1 (C(1)); 72.0 (d, J_{C-P} = 6.9 Hz); 71.7; 70.1; 69.7; 67.9; 63.1 (d, J_{C-P} = 5.3 Hz); 60.60 (d, J_{C-P} = 3.8 Hz); 31.5-13.4 (C alkyl).

Examples of preparation of monoesters of phosphonoformic acid according to the procedure described under "Preparation of monoesters of phosphonoformic acid":

Example 28

Disodium *n*-octadecyl α-D-glucopyranosid-6-yl carboxyphosphonate:

500 mg of *n*-octadecyl 2,3,4-tri-O-benzoyl–α–D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate (0.568 mmoles) gave after reverse phase chromatography (gradient H_2O, H_2O/ MeOH: 1/4) 190 mg (57%) of the title compound.

R_f = 0.06 (AcOEt/MeOH/H_2O: 7/2/1).

^{1}H-NMR (D_2O): 4.84 (d, J= 2.8 Hz, H-C(1)); 4.24 (t, J= 9.8); 3.94 (m, 1H); 3.73-3.52 (m, 5H); 3.39 (m, 1H); 1.56 (m, 2H); 1.35-1.18 (m, 30H); 0.82 (m, 3H).

^{13}C -NMR (D_2O): 178.5 (d, J_{CO-P} = 230 Hz); 99.7 (C(1)); 73.4; 72.4; 71.9 (*br.*s); 69.6; 69.5 (*br.*s); 67.5; 64.1 (*br.*s); 33.0-14.9 (C alkyl).

Example 29

Disodium *cis*-9-octadecen-1-yl α-D-glucopyranosid-6-yl carboxyphosphonate:

500 mg of *cis*-9-octadecen-1-yl 2,3,4-tri-O-benzoyl–α–D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate (0.569 mmoles) gave after reverse phase chromatography (gradient H_2O, H_2O/ MeOH: 1/4) 176 mg (53%) of the title compound.

R_f = 0.06 (AcOEt/MeOH/H_2O: 7/2/1).

^{1}H-NMR (D_2O): 5.28 (m, 2H olef.); 4.81 (*br.*s, H-C(1)); 4.22 (m, 1H); 3.93 (m, 1H); 3.68-3.49 (m, 5H); 3.38 (m, 1H); 1.95 (m, 4H); 1.54 (m, 2H); 1.24-1.16 (m, 22H); 0.83 (m, 3H).

^{13}C -NMR (D_2O): 177.7 (d, J_{CO-P} = 232 Hz); 100 (C(1)); 73.7; 72.8; 70.2 (d, J_{C-P} = 6.9 Hz); 69.8 (2C); 64.4 (d, J_{C-P} = 3.8 Hz); 35.4-15.2 (C alkyl).

Example 30

Disodium *trans*-9-octadecen-1-yl α-D-glucopyranosid-6-yl carboxyphosphonate:

737 mg of *trans*-9-octadecen-1-yl 2,3,4-tri-O-benzoyl–α–D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate (0.838 mmoles) after reverse phase chromatography (gradient H_2O, H_2O/ MeOH: 1/4) 153 mg (31%) of the title compound.

R_f = 0.06 (AcOEt/MeOH/H_2O: 7/2/1).

^{1}H-NMR (D_2O): 5.30 (m, 2H olef.); 4.82 (*br.*s, H-C(1)); 4.22 (m, 1H); 3.93 (m, 1H); 3.69-3.38 (m, 6H);1.94-1.89 (m, 4H); 1.55 (m, 2H); 1.27-1.18 (m, 22H); 0.79 (m, 3H).

^{13}C -NMR (D_2O): 187.7 (d, J_{CO-P} = 232 Hz); 100 (C(1)); 73.7; 72.8; 70.2 (d, J_{C-P} = 6.9 Hz); 69.8 (2C); 64.4 (d, J_{C-P} = 3.8 Hz); 35.4-15.2 (C alkyl).

Example 31

Disodium *n*-tetradecyl α-D-glucopyranosid-6-yl carboxyphosphonate:

(35 ml THF was used) 413 mg of *n*-tetradecyl 2,3,4-tri-O-benzoyl–α–D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate (0.50 mmoles) gave, after flash chromatography, (MeOH/H_2O : 3/1) 180 mg (71%) of the title compound.

R_f = 0.34 (MeOH/H_2O 3/1).

^{1}H-NMR (D_2O): 4.82 (d, H-C(1)); 4.24 (t, 1H); 3.97 (m, 1H); 3.74-3.50 (m, 6H); 3.41 (1H); 1.59 (m, 2H); 1.4-1.2 (m, 22H); 0.82 (m, 3H).

^{13}C-NMR (D_2O, (ref. CD_3OD 49.0 ppm)): 178.4 (d, J_{CO-P}= 232 Hz); 99.6 (C(1)); 73.4; 72.4; 71.9 (d, J_{C-P} =6.9 Hz); 69.4; 69.5; 64.2 (d, J_{C-P} =4.6 Hz); 32.7-14.7 (C alkyl).

^{31}P-NMR (D_2O, H-coupled, (ref. H_3PO_4 0 ppm)): 1.49 (s).

Example 32

Disodium *n*-tetradecyl β-D-glucopyranosid-6-yl carboxyphosphonate:

(8 ml THF was used) 303 mg of *n*-tetradecyl 2,3,4-tri-O-benzoyl-β-D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate (0.37 mmoles) gave after flash chromatography ($MeOH/H_2O$: 3/1) 174 mg (93%) of the title compound.

R_f = 0.19 ($MeOH/H_2O$: 3/1)

^{1}H-NMR (D_2O): 4.43 (d, J= 2.8 Hz, H-C(1)); 4.24 (t, J= 9.8); 3.90 (m, 1H); 3.64-3.42 (m, 6H); 3.29 (m, 1H); 1.6 (m, 2H); 1.4-1.2 (m, 22H); 0.82 (m, 3H).

^{13}C -NMR (D_2O): 178.5 (d, J_{CO-P} = 232 Hz); 100.0 (C(1)); 72.6; 72.3 (d, J_{C-P} = 6.1 Hz); 70.7; 68.2; 66.2; 60.7 (d, J_{C-P} =5.4 Hz); 28.9-11.0 (C alkyl).

Example 33

Disodium *n*-dodecyl α-D-glucopyranosid-6-yl carboxyphosphonate:

1.285 mg of *n*-dodecyl 2,3,4 tri-O-benzoyl-α-D-glucopyranosid-6-yl (ethoxycarbonyl)phosphonate (1.612 mmoles) gave after reverse phase chromatography (gradient H_2O, H_2O/ MeOH: 1/4) 532 mg (66 %) of the title compound.

R_f = 0.06 (AcOEt/MeOH/H_2O: 7/2/1).

^{1}H-NMR (D_2O): 4.78 (d, J= 3.6 Hz, H-C(1)); 4.10 (m, 1H); 3.92 (*br*.dd, J= 11.1, 3.7 Hz, H-C(6)); 3.63-3.49 (m, 4H); 3.46 (dd, J= 9.8, 3.6 Hz, H-C(2)); 3.38 (dt, J= 9.7, 6.6 Hz); 1.50-1.46 (m, 2H); 1.16 (m, 18H); 0.75 (t, J= 6.8 Hz, 3H).

^{13}C -NMR (D_2O): 176.2 (d, J_{CO-P} = 233 Hz); 97.2 (C(1)); 71.4; 70.2; 69.7 (d, J_{C-P} = 6.9 Hz); 67.5; 67.3; 62.0 (d, J_{C-P} = 5.4 Hz); 30.2-12.4 (C alkyl).

Example 34

Disodium eicosyl β-D-galactopyranosid-6-yl carboxyphosphonate:

700 mg of eicosyl 2,3,4-tri-O-benzoyl-β-D-galactopyranosid-6-yl (ethoxycarbonyl)phosphonate (0.77 mmoles) gave after reverse phase chromatography (gradient H_2O, H_2O/ MeOH: 1/4) 170 mg (36 %) of the title compound.

R_f = 0.06 (AcOEt/MeOH/H_2O: 7/2/1).

^{1}H-NMR (D_2O): 4.91 (d, J= 7.1 Hz, H-C(1)); 4.31 (m, H-C(6)); 4.03 (m, H-C(6)); 3.79-3.46 (m, 6H); 1.61-1.55 (m, 2H); 1.48-1.38 (m, 34H); 0.85 (t, J= 6.8 Hz, 3H).

^{13}C -NMR (D_2O): 178.8 (d, J_{CO-P} = 231 Hz); 101.1 (C(1)); 73.7; 72.7; 72.2 (d, J_{C-P} = 6.9 Hz); 69.8 (2C); 64.5 (*br.*s); 33.9-15.2 (C alkyl).

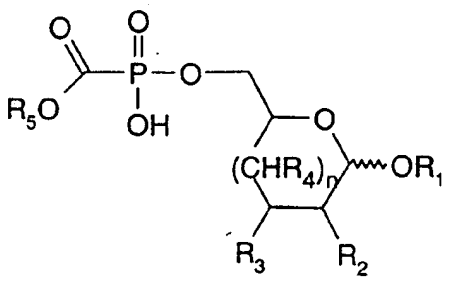
Tests for antiviral activity

The antiviral activity of the compounds of the invention may be determined according to the method of Wahren, B. et al. J. Virol. Methods 6, (1983) 141-149. Thus confluent human lung fibroblast cells are infected with Herpes simplex virus type 1 (HSV-1). After absorption for one hour at 37°C, virus is removed and antiviral drugs diluted in cell media were added, at concentrations of 800 µM down to 3 µM. Cells are incubated at 37 °C in a humidified atmosphere of 5% CO_2 in air until characteristic cytopathic effect is seen in control wells (24-48 h). Cells are lysed by addition of Triton X-100, and viral antigen content of the supernatants measured by enzyme-linked immunosorbent assay (ELISA) using a monoclonal antibody.

The title compounds of Examples 28 to 34 were tested according to this test method for antiviral activity and were all found to be active.

Claims

1. A compound of the formula I



I

wherein the wavy line signifies a bond which is either in the α- or in the β-configuration;

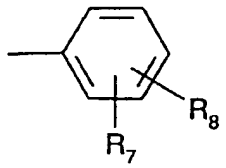
n is 0 or 1;

R_1 is C_{1-24}-alkyl, C_{2-24}-alkenyl, C_{2-24}-alkapolyenyl containing 2 to 6 double bonds, C_{2-24}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-24}-alkyl, or C_{1-12}-alkoxy-C_{1-12}-alkyl group, all of which may be branched or unbranched and all of which may be optionally substituted with hydroxy, amino, halogen, or oxo;

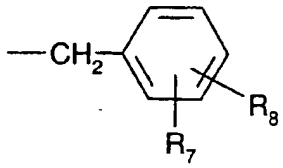
R_2, R_3 and R_4 are each independently hydrogen, halogen, amino, acetylamino, azido, or a group XR_6 wherein X is O or S and R_6 is hydrogen, a branched or unbranched C_{1-4}-alkyl or C_{2-4}-alkenyl group both of which may be optionally substituted with hydroxy, amino, halogen, or oxo, or

R_2, R_3 and R_4 together with the respective geminal hydrogen represent an oxo group;

R_5 is hydrogen, or R_5 is a phenyl group of the formula II or III,



II



III

wherein R_7 and R_8 are the same or different and are bound to any two positions of the phenyl ring and each is selected from the group consisting of hydrogen, halogen, or C_{1-4}-alkyl, C_{1-4}-alkoxy, C_{1-4}-acyl, C_{1-4}-acyloxy, C_{2-5}-alkoxycarbonyl all of which may be branched or unbranched; or R_7 and R_8 together form an unbranched saturated alkylene chain having 3 or 4 carbon atoms bound to adjacent positions, i.e. 2,3- or 3,4- in the phenyl ring; or R_7 and R_8 together form a methylenedioxy group, a 1,1-ethylidenedioxy group, or a 1,2-ethylenedioxy group bound to the 2,3- or 3,4-positions of the phenyl ring,

or R_5 is a group $R_9COOCHR_{10}-$ or a group $R_9OCOOCHR_{10}-$

wherein R_9 is C_{1-6}-alkyl, C_{2-6}-alkenyl, C_{2-6}-alkynyl, C_{3-8}-cycloalkyl, C_{3-8}-cycloalkyl-C_{1-6}-alkyl, or C_{1-6}-alkoxy-C_{1-6}-alkyl group all of which may be branched or unbranched, which is optionally substituted with hydroxy, amino, halogen, or oxo; and R_{10} is hydrogen or a branched or unbranched C_{1-4}-alkyl group;

and wherein the configurations of the substituents R_2, R_3, R_4 and $R_5OOCPO(OH)OCH_2$- in I independently are D-gluco, L-gluco, D-galacto, L-galacto, D-manno, L-manno, D-talo, L-talo, D-allo, L-allo, D-altro, L-altro, D-gulo, L-gulo, D-ido, or L-ido when n is 1, or that the configurations of the substituents R_2, R_3 and $R_5OOCPO(OH)OCH_2$- in I independently are D-ribo, L-ribo, D-arabino, L-arabino, D-xylo, L-xylo, D-lyxo, or L-lyxo when n is 0;

and physiologically acceptable salts and optical isomers thereof.

2. A compound according to claim 1 wherein R_1 is a C_{9-24}-alkyl, C_{9-24}-alkenyl, C_{9-24}-alkapolyenyl containing 2 to 6 double bonds, C_{9-24}-alkynyl, C_{3-8}-cycloalkyl-C_{6-24}-alkyl, or C_{1-12}-alkoxy-C_{8-12}-alkyl group.

3. A compound according to either of claims 1 or 2 wherein R_2, R_3 and R_4 are each a hydroxyl group.

4. A compound according to any one of claims 1 to 3 wherein R_5 is hydrogen.

5. A compound according to any one of claims 1 to 4 wherein the configuration of the glycosidic bond is α-.

6. A compound according to any one of claims 1 to 4 wherein the configuration of the glycosidic bond is β-.

7. A compound according to any one of claims 1 to 6 wherein n is 1.

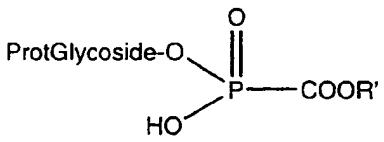
8. A compound of the formula I according to any one of claims 1 to 7 wherein the configuration of the substituents R_2, R_3, R_4 and $R_5OOCPO(OH)OCH_2$- is D-gluco.

9. A compound according to any one of claims 1 to 8 wherein R_1 is *n*-tetradecyl;

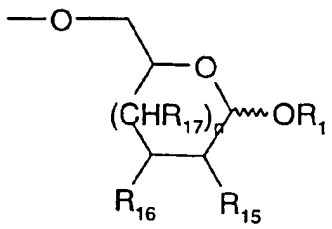
n-octadecyl; *trans*-9-octadecen-1-yl, or *cis*-9-octadecen-1-yl.

10. A process for the preparation of a compound of formula I according to claim 1, carrying at least one group capable of protection, characterized by

deprotection of a compound of the formula



wherein R' has the meaning given above for R_5 with the exception of hydrogen, or R' is branched or unbranched C_{1-6}-alkyl, and ProtGlycoside-O- corresponds to a group of the formula



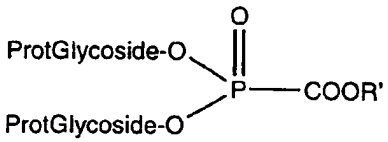
wherein n is 0 or 1, R_1 has the meaning given above and R_{15}, R_{16} and R_{17} each correspond to the groups R_2, R_3 and R_4, respectively, which have been derivatized by suitable protective groups where appropriate.

11. A process according to claim 10 wherein R_{15}, R_{16} and R_{17} each correspond to the groups R_2, R_3 and R_4, respectively, at least one or more of which have been derivatized where appropriate by methoxymethyl, methylthiomethyl, benzyloxymethyl,*p*-methoxybenzyloxymethyl, tetrahydropyranyl, 1-ethoxyethyl, 2,2,2-trichloroethyl, 2-

trimethylsilylethyl, *t*-butyl, allyl, but-2-enyl, 3-methylbut-2-enyl, *p*-methoxyphenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *p*-nitrobenzyl, diphenylmethyl, trimethylsilyl, triethylsilyl, *t*-butyldimethylsilyl, acetyl, chloroacetyl, trifluoroacetyl, propionyl, isobutyryl, pivaloyl, benzoyl, *p*-methoxybenzoyl, *p*-chlorobenzoyl, *p*-bromobenzoyl, 2,2,2-trichloroethoxycarbonyl, methanesulfonyl or *p*-toluenesulfonyl in the case where at least one of the groups R_2, R_3 and R_4 is a hydroxyl group, or R_6 is substituted by a hydroxyl group, or ethylidene, isopropylidene, cyclohexylidene, benzylidene, *p*-methoxybenzylidene, methoxymethylene, ethoxymethylene, di-*t*-butylsilylene, or tetraisopropyldisiloxane-1,3-diylidene in the case where at least two of groups R_2, R_3 and R_4 are hydroxyl groups, or methoxymethyl, benzylthiomethyl, phenylthiomethyl, tetrahydropyranyl, 2-cyanoethyl, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, diphenylmethyl, *t*-butyl, acetyl, benzoyl, 2,2,2-trichloroethoxycarbonyl, *t*-butoxycarbonyl or benzyloxycarbonyl in the case where at least one of the groups R_2, R_3 and R_4 is a thiol group, or ethoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, *t*-butoxycarbonyl, allyloxycarbonyl, benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, formyl, chloroacetyl, trichloroacetyl, trifluoroacetyl, phthaloyl, allyl, 2-trimethylsilylethoxymethyl, benzyl, benzylidene or *p*-methoxybenzylidene in the case where at least one of the groups of the groups R_2, R_3 and R_4 is an amino group, or R_6 is substituted by an amino group, or finally, in the case where one of the groups R_2, R_3 and R_4 together with the respective geminal hydrogen represents oxo, or R_6 is substituted by an oxo group, then the group is derivatized as e.g. a dimethyl ketal, a bis(2,2,2-trichloroethyl) ketal, a dibenzyl ketal, a diacetyl ketal, a 1,3-dioxane, a 5-methylene-1,3-dioxane, a 1,3-dioxolane, a S,S'-dimethyl dithioketal, a S,S'-dibenzyl dithioketal, a S,S'-diacetyl dithioketal, a 1,3-dithiane, a 1,3-dithiolane, a 1,3-oxathiolane, an O-acetyl cyanohydrin, an O-trimethylsilyl cyanohydrin, an N,N-dimethylhydrazone, a 2,4-dinitrophenylhydrazone, an oxime, or an O-methyloxime.

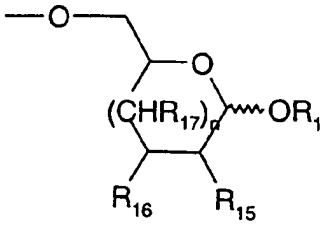
12. A process for the preparation of compounds of the formula I as defined in claim 1, characterized by

A. Selective removal of one of the protected glycoside groups of a compound of the formula



wherein R' has the meaning given above for R_5 with the exception of hydrogen, or R' is branched or unbranched C_{1-6}-alkyl;

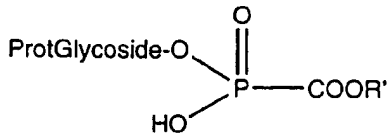
ProtGlycoside-O- corresponds to a group of the formula



wherein n is 0 or 1, R_1 has the meaning given above and R_{15}, R_{16} and R_{17} each correspond to the groups R_2, R_3 and R_4, respectively, which have been derivatized where appropriate by methoxymethyl, methylthiomethyl, benzyloxymethyl,*p*-methoxybenzyloxymethyl, tetrahydropyranyl, 1-ethoxyethyl, 2,2,2-trichloroethyl, 2-trimethylsilylethyl,*t*-butyl, allyl, but-2-enyl, 3-methylbut-2-enyl, *p*-methoxyphenyl, benzyl, *p*-methoxybenzyl, 3,4-dimethoxybenzyl, *p*-nitrobenzyl, diphenylmethyl, trimethylsilyl, triethylsilyl,*t*-butyldimethylsilyl, acetyl, chloroacetyl, trifluoroacetyl, propionyl, isobutyryl, pivaloyl, benzoyl, *p*-methoxybenzoyl, *p*-chlorobenzoyl, *p*-bromobenzoyl, 2,2,2-trichloroethoxycarbonyl, methanesulfonyl or *p*-toluenesulfonyl in the case where at least one of the groups R_2, R_3 and R_4 is a hydroxyl group, or R_6 is substituted by a hydroxyl group, or ethylidene, isopropylidene, cyclohexylidene, benzylidene,*p*-methoxybenzylidene, methoxymethylene, ethoxymethylene, di-*t*-butylsilylene, or tetraisopropyldisiloxane-1,3-di-ylidene in the case where at least two of groups R_2, R_3 and R_4 are hydroxyl groups, or

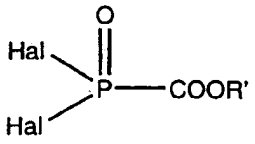
methoxymethyl, benzylthiomethyl, phenylthiomethyl, tetrahydropyranyl, 2-cyanoethyl, benzyl, *p*-methoxybenzyl, *p*-nitrobenzyl, diphenylmethyl, *t*-butyl, acetyl, benzoyl, 2,2,2-trichloroethoxycarbonyl, *t*-butoxycarbonyl or benzyloxycarbonyl in the case where at least one of the groups R_2, R_3 and R_4 is a thiol group, or ethoxycarbonyl, 9-fluorenylmethoxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, *t*-butoxycarbonyl, allyloxycarbonyl, benzyloxycarbonyl, *p*-methoxybenzyloxycarbonyl, *p*-nitrobenzyloxycarbonyl, formyl, chloroacetyl, trichloroacetyl, trifluoroacetyl, phthaloyl, allyl, 2-trimethylsilylethoxymethyl, benzyl, benzylidene or *p*-methoxybenzylidene in the case where at least one of the groups of the groups R_2, R_3 and R_4 is an amino group, or R_6 is substituted by an amino group, or finally, in the case where one of the groups R_2, R_3 and R_4 together with the respective geminal hydrogen represents oxo, or R_6 is substituted by an oxo group, then the group is derivatized as a dimethyl ketal, a bis(2,2,2-trichloroethyl) ketal, a dibenzyl ketal, a diacetyl ketal, a 1,3-dioxane, a 5-methylene-1,3-dioxane, a 1,3-dioxolane, a S,S'-dimethyl dithioketal, a S,S'-dibenzyl dithioketal, a S,S'-diacetyl dithioketal, a 1,3-dithiane, a 1,3-dithiolane, a 1,3-oxathiolane, an O-acetyl cyanohydrin, an O-trimethylsilyl cyanohydrin, an N,N-dimethylhydrazone, a 2,4-dinitrophenylhydrazone, an oxime, or an O-methyloxime;

to give a compound of the formula

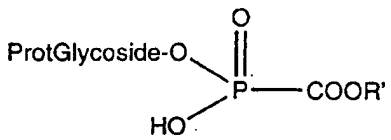


and, optionally, final deprotection with or without removal of R' to give, except where R' is branched or unbranched C_{1-6}-alkyl, a compound of the formula I.

B. Reaction of one equivalent of a compound of the formula



wherein R' has the meaning given above for R_5 with the exception of hydrogen, or R' is branched or unbranched C_{1-6}-alkyl and Hal is Cl, Br, or I with one equivalent or less of a glycoside ProtGlycoside-OH, which may be suitably protected, with a free hydroxyl group at the 6-position if a hexose or at the 5-position if a pentose, wherein ProtGlycoside-O- is defined as above in A, in the absence of base to give a compound of the formula



and, optionally, final deprotection with or without removal of R' to give, except where R' is branched or unbranched C_{1-6}-alkyl, a compound of the formula I.

13. A compound according to any one of claims 1 to 9 for use in therapy.

14. A compound according to any one of claims 1 to 9 for use in the treatment of viral infections in mammals.

15. A compound according to any one of claims 1 to 9 for use in the treatment of human herpesvirus or human retrovirus infections.

16. A compound according to any of claims 1 to 9 for use in the treatment of viral infections in humans caused by HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, HHV-7, HHV-8, HIV-1, HIV-2, HTLV-1 or HTLV-2.

17. Use of a compound according to any one of claims 1 to 9 in the manufacture of a pharmaceutical formulation for the treatment of viral infections in mammals.

18. Use of a compound according to any one of claims 1 to 9 in the manufacture of a pharmaceutical formulation for the treatment of human herpesvirus or retrovirus infections.

19. Use of a compound according to any one of claims 1 to 9 in the manufacture of a pharmaceutical formulation for the treatment of viral infections in humans caused by HSV-1, HSV-2, VZV, CMV, EBV, HHV-6, HHV-7, HHV-8, HIV-1, HIV-2, HTLV-1 or HTLV-2.

20. A pharmaceutical composition containing as an active ingredient a compound as defined in any one of claims 1 to 9.

21. A pharmaceutical composition according to claim 20 which is suitable for oral administration.

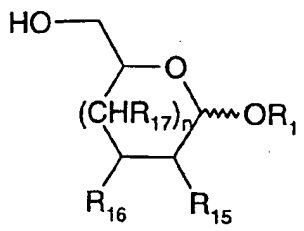
22. A pharmaceutical composition according to claim 20 which is suitable for parenteral administration.

23. A pharmaceutical composition according to claim 20 which is suitable for rectal administration.

24. A pharmaceutical composition according to claim 20 which is suitable for topical administration.

25. A method of treatment of virus infections wherein a therapeutically active amount of a compound according to any one of claims 1 to 9 is administered to a patient in need of such treatment.

26. A compound of the formula V



V

wherein the wavy line signifies a bond which is either in the α- or in the β-configuration;

wherein n is 0 or 1, R_1 is C_{9-24}-alkyl, C_{9-24}-alkenyl, C_{9-24}-alkapolyenyl containing 2 to 6 double bonds, C_{9-24}-alkynyl, C_{3-8}-cycloalkyl-C_{6-24}-alkyl, or C_{1-12}-alkoxy-C_{8-12}-alkyl group, all of which may be branched or unbranched and all of which may be optionally substituted with hydroxy, amino, halogen, or oxo;

and wherein R_{15}, R_{16} and R_{17} each correspond to the groups R_2, R_3 and R_4, respectively, which have been derivatized by suitable protective groups,

provided that in the case where the configuration of the substituents R_{15}, R_{16} , R_{17} and $HOCH_2$- is D-gluco,

i) R_1 is not *n*-decyl, *n*-dodecyl, or *n*-octadecyl at the same time as each of R_{15}, R_{16} , and R_{17} is benzyloxy, and

ii) R_1 is not 1-ethenyl-1,5-dimethyl-4-hexen-1-yl at the same time as each of R_{15}, R_{16} and R_{17} is benzoyloxy, and

iii) R_1 is not 8-hydroxy-1-(4-hydroxy-2-methyl-2-butenyl)-3,7-dimethyl-2,6-octadienyl at the same time as R_{15} is 2-methyl-2-butenoate and each of R_{16} and R_{17} is acetoxy, and

provided that, in the case where the configuration of the substituents R_{15}, R_{16} , R_{17} and $HOCH_2$- is D-galacto,

iv) R_1 is not *n*-octadecyl at the same time as each of R_{15} , R_{16} and R_{17} is acetoxy, and

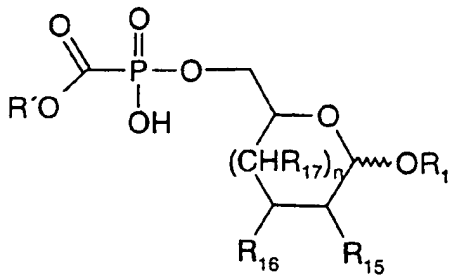
provided that in the case where the configuration of the substituents R_{15}, R_{16}, R_{17} and $HOCH_2$- is D-manno,

v) R_1 is not *n*-hexadecyl at the same time as each of R_{15} , R_{16} and R_{17} is trimethylsilyloxy, and

vi) R_1 is not 3,7,11-trimethyl-2,6,10-dodecatrienyl at the same time as each of R_{15} , R_{16} and R_{17} is acetoxy,

and salts and optically active isomers thereof.

27. A compound of the formulaVI



VI

wherein the wavy line, n, and R_1 are as defined in Claim 1,

and wherein R_{15}, R_{16} and R_{17} each correspond to the groups R_2, R_3 and R_4, respectively, as defined in Claim 1, which have been derivatized by suitable protective groups,

R' is as defined in Claim 10,

and physiologically acceptable salts and optical isomers thereof.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 97/01668

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: C07H 11/04, C07H 13/04, C07F 9/655, A61K 31/70
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: C07H, C07F, A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI, IFIPAT

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 9639831 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA), 19 December 1996 (19.12.96) --	1-24,27
A	WO 9615132 A1 (THE REGENTS OF THE UNIVERSITY OF CALIFORNIA), 23 May 1996 (23.05.96) --	1-24,27
A	WO 9413682 A1 (VESTAR, INC.), 23 June 1994 (23.06.94) -- --------	1-24,27

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 1998	24 -02- 1998
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Eva Johansson Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/ SE 97/01668

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 25
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [X] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1-25, 27

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Claims 1-27

1) Claims 1-25 and 27 concerning phosphonoformic acid derivatives, process for their preparation and intermediates containing phosphonoformic acid.

2) Claim 26 concerning ProtGlycoside-OH derivatives.

ProtGlycoside-OH in claim 26 can be used as an intermediate for different endproducts and not specific to the endproduct according to claim1. The technical relationship between the endproduct and the intermediate is lacking and that leads to lack of unity.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/SE 97/01668

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9639831 A1	19/12/96	AU 6171796 A	30/12/96
WO 9615132 A1	23/05/96	AU 4163596 A	06/06/96
		EP 0792275 A	03/09/97
		US 5696277 A	09/12/97
WO 9413682 A1	23/06/94	AU 680812 B	14/08/97
		AU 3328793 A	04/07/94
		EP 0674646 A	04/10/95
		JP 8504439 T	14/05/96
		US 5194654 A	16/03/93
		US 5411947 A	02/05/95
		US 5463092 A	31/10/95
		US 5484809 A	16/01/96